CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201635Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD
Subject	(Acting) Division Director Summary Review
NDA/BLA # **Supplement #**	201,635
Applicant Name	Supernus Pharmaceuticals
Date of Submission	June 17, 2013
PDUFA Goal Date	August 18, 2013
Proprietary Name / **Established (USAN) Name**	Trokendi XR (topiramate) Extended-Release
Dosage Forms / Strength	Capsule / 25mg, 50mg, 100 mg, and 200 mg
Proposed Indication(s)	1. Partial Onset Seizures (monotherapy in patients 10 years of age and older and adjunctive treatment in patients 6 years of age and older) 2. Primary Generalized Tonic-Clonic Seizures (monotherapy in patients 10 years of age and older and adjunctive treatment in patients 6 years of age and older) 3. Seizures Associated with Lennox- Gastaut Syndrome (adjunctive treatment in patients 6 years of age and older).
Action	Approval

NDA 201,635, for the use of Trokendi XR (topiramate) Extended-Release Capsules as adjunctive and monotherapy of partial and generalized tonic-clonic seizures and the seizures of Lennox-Gastaut syndrome, was issued a tentative approval letter on June 7, 2013, because of the existence of protected information in the labeling of the reference listed drug (Topamax) that provides safety information necessary for safe use in patients 1 to 24 months of age. I refer the reader to the summary memos from Dr. Katz dated June 21, 2012, and June 7, 2013, in which the basis for tentative approval is described.

The sponsor sent a complete response on June 17, 2013, in which he indicated that the protected information expired on June 22, 2013. There were no other changes to the application. Therefore, I will issue an approval letter for NDA 201,635. This letter will include required postmarketing studies (PMRs) in the pediatric population.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
08/16/2013

MEMORANDUM

DATE: June 7, 2013

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 201635

SUBJECT: Action Memo for NDA 201635, for the use of Trokendi XR (topiramate) Extended-Release Capsules as adjunctive and monotherapy of partial and generalized tonic-clonic seizures and the seizures of Lennox-Gastaut syndrome

NDA 201635, for the use of Trokendi XR (topiramate) Extended-Release Capsules as adjunctive and monotherapy of partial and generalized tonic-clonic seizures and the seizures of Lennox-Gastaut syndrome, was submitted by Supernus Pharmaceuticals, Inc., on 1/13/1; this submission was not filed due to numerous deficiencies. It was subsequently re-submitted on 8/30/11 and filed.

The division issued a Tentative Approval (TA) letter on 6/25/12. In brief, the sponsor proposed a novel pharmacokinetic (PK) approach comparing plasma levels of this once a day formulation to the innovator Topamax (which is given twice a day) that the division found persuasive as evidence that the two products would result in equivalent effectiveness. For this reason, the division was prepared to approve the product without a controlled trial. However, the sponsor of Topamax had previously performed a study in pediatric patients (1 month to 2 years of age) that resulted in important safety information being added to the label of that product. We had determined that this information had to be included in the Trokendi XR label in order for that product to be used safely; however, these data were considered protected information, and we were precluded from including a description of these data in the Trokendi XR label until the protection expired (date of expiration of this protection is June 22, 2013). Because we had concluded that these data must be described in Trokendi XR labeling, but were prevented from doing so until June 22, 2013, we issued a TA letter for the Trokendi XR application on 6/25/12 (see my memo of 6/25/12 for a more detailed description of these issues).

Agency staff met with the sponsor on 10/3/12 to discuss our rationale for requiring that the pediatric data be included in the Trokendi XR label. Subsequent to that meeting, the sponsor made a submission in which they argued that the pediatric data did not need to be included in product labeling; in that submission, they also provided alternative language for labeling that they believed would suffice as a description of the risks in infants (this submission was reviewed extensively and in detail by Jeanine Best of the Pediatric and Maternal Health Staff). The Agency found those arguments and alternative language

inadequate, and issued a letter to the sponsor on 1/17/13 that described, in detail, our reasons for this finding.

The sponsor formally responded to the TA letter in a submission dated 12/4/12. The PDUFA date for action on this application is 6/7/13. This response included changes to various packaging presentations (30-count blister package (b) (4)) as well as a proposal to change to a new secondary package manufacturer for portions of the blister packages. In addition, the sponsor again argues for approval prior to the expiration of the protected pediatric labeling language.

The re-submission has been reviewed by Dr. Julie Neshiewat, Division of Medication Error Prevention and Analysis; Dr. Thomas M. Wong, Office of New Drug Quality Assessment; and Dr. Norman Hershkowitz, neurology team leader and Cross-Discipline Team Leader (CDTL). The review team has concluded that the application could otherwise be approved, but for the issue of the required, but still protected, pediatric labeling language.

I agree that the application could otherwise be approved, but we cannot do so until the expiration of the protection of the pediatric safety data, a description of which we still believe must be included in the Trokendi XR label. For these reasons, then, I will issue the attached, second TA letter, with appended labeling.

Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
06/07/2013

Cross-Discipline Team Leader Review

Date	June 5, 2013
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	201635
Applicant	Supernus Pharmaceuticals
Date of Submission	December 4, 2012
PDUFA Goal Date	June 7, 2013
Proprietary Name / Established (USAN) names	Topiramate XR/ Trokendi XR
Dosage forms / Strength	Capsules 25, 50, 100, and 200 mg
Proposed Indication(s)	1. Partial Onset Seizures (monotherapy in patients $\geq$ 10 years and adjunctive treatment in patients $\geq$ 6 years) 2. Primary Generalized Tonic-Clonic Seizures (monotherapy in patients > 10 years and adjunctive treatment in patients > 6 years) 3. Seizures Associated with Lennox- Gastaut Syndrome (adjunctive treatment in patients > 6 years).
Recommended:	Tentative Approval

1. Introduction and Background

Trokendi XR is an extended release formulation of the referenced label drug Topamax (topiramate) that is designed to be used once daily. Topamax is labeled for twice daily use. Topamax is presently approved for monotherapy and adjunctive therapy for seizures classified as partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) in patients older 2 years and above as well as adjunctive treatment in patients with seizures associate with Lennox-Gastaut syndrome (LGS) in patients 2 years and above. In the first supplement to this IND, the Sponsor requested approval for Trokendi's seizure indications, based upon a PK analysis where they demonstrated that not only did it meet traditional bioequivalence standards, but that upon analysis of multiple concentrations time points and cumulative AUCs over a 24 hour period at steady state it also met a similar statistical standard for bioequivalence. The Division found the argument convincing and agreed that an approval should be given. However, because there was still patent protected information in the proprietary label regarding safety outcomes in 1 to 24 month old children and the carve out of theis crucial information could not be legally performed, a tentative approval action was made.

The Sponsor has now provided a "Request for Final Approval. There is no substantive change in the application, but there are changes in the 30-count blister package (b) (4) The layout of these packages has been under discussions with the Division since the first tentative approval. In this application the Sponsor has changed to a new secondary package manufacturer (b) (4) Also included in this application is a brief argument for approval of the application prior to the time that exclusivity of pediatric information expires. A safety update is also included.

2. CMC/Device

The CMC reviewer was Dr. T.M. Wong. He notes that the new blister packaging, which essentially uses the same material as the prior packaging, is acceptable without further testing. Also noted by the chemistry reviewer the Sponsor submitted additional 18, 24 and 30 months stability data at 25°C/60% RH storage conditions on all capsules strengths at both bottle and blister packages and that the post-approval stability monitoring commitment has been revised to contain the 30 month testing time point. The reviewer recommends approval. A 30 month expiry is granted.

3. Nonclinical Pharmacology/Toxicology

Not applicable.

4. Clinical Pharmacology/Biopharmaceutics

Not Applicable.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

Not applicable.

7. Safety

The Sponsor provided a brief ISS for this application. There does not appear to be any new significant data, which did not appear in the prior submission that led to the Tentative Approval action. Prior conclusions regarding safety of this compound remain unchanged.

8. Advisory Committee Meeting

Not Applicable.

9. Pediatrics

See prior CDTL review.

10. Other Relevant Regulatory Issues

As noted above in the cover letter to this application, the Sponsor submitted a legal and policy argument as to why they should be permitted to market the product in spite of the exclusivity protection for the pediatric safety information. This was dealt with outside of this NDA submission. The Division met with the Sponsor on October 3, 2012, at which that time the Sponsor was requested to submit an argument and labeling that they considered could be approved. This was submitted on October 31, 2012 and reviewed by Jeannine Best on January 15, 2013. Following this review and additional consultation with others on the Trokendi group a letter issues on January 17, 2013, that concluded that:

> "For safety reasons, to convey this pediatric information, you must include the protected Topamax pediatric use language in the Trokendi XR labeling or propose alternative language to fully address the issues above."

As noted in the Introduction/Background section to this review, a large part of this application involved new blister packaging. This was reviewed by CMC (see above) and Julie Neshiewat, of DMEPA. Dr. Neshiewat concluded in her review, dated May 16, 2013:

> "… that the revised container labels are acceptable; however, the proposed blister pack labeling can revised to improve the readability and prominence of important information on the labeling as well as add clarifying information to ensure proper use of the blister packaging."

A number of items were enumerated. The Sponsor adequately responded, as per Dr. Neshiewat, to most items, although a formal review is not yet available. Two items remain. These items are as follows:

> "Blister Pack Labeling: (b) (4) Retail 30-count
> 1. For increased prominence, bold the portion "per capsule" in the statement "XX mg percapsule" found inside of the highlighted circle for strength statement.
> B. Blister Pack Labeling: Retail 30-count
> 1. On the panel that contains "Instructions to Open Blister Card" and "Instructions to Remove Capsules," relocate the strength statement from the left of the proprietary name and established name to below the proprietary name and established name for consistency with other panels."

The Sponsor has not yet responded to these items, but they are not considered issues that would bar an action of approval.

11. Labeling

The Sponsor has made minor formatting and grammatical changes to the label. This reviewer examined these and, except for one minor exception, accepted all. The Sponsor agreed with these edits and the label will be included with the letter.

12. Recommendations/Risk Benefit Assessment

As noted above the required safety information is still protected. This exclusivity expires on June 22, 2013. As a result the action remains that of a Tentative Approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN HERSHKOWITZ
06/07/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Confidential Memorandum

Date: June 25, 2012

From: Dr. Russell Katz, Director, Division of Neurology Products, ODE I

To: File for NDA 201-635

Re: Tentative approval of Trokendi XR (extended-release topiramate), NDA 201-635

On this date, the Food and Drug Administration (FDA or the Agency) issued a tentative approval of Supernus Pharmaceuticals' new drug application (NDA) 201-635 for Trokendi XR (extended-release topiramate). Also on this date, FDA responded to the citizen petition submitted on December 28, 2011 by Upsher-Smith Laboratories (USL or Petitioner), FDA-2011-P-0931 (Petition).

USL is also seeking approval of an extended release (ER) version of topiramate. The Petition alleges that because the Agency requested that USL conduct a clinical efficacy study to support approval of its 505(b)(2) NDA for ER topiramate, it would be "inequitable and inconsistent" to approve another sponsor's application for ER topiramate without such a study (Petition at 1). The Petitioner specifically argues that if FDA were to approve Supernus's 505(b)(2) NDA for ER topiramate without data from a clinical efficacy study, this would constitute disparate treatment of similarly situated parties in violation of the Administrative Procedure Act (APA) (Petition at 5-6). Therefore, the Petitioner requests that FDA refrain from approving any application for ER topiramate (including Supernus's application), regardless of the indication, that does not include an adequate and well-controlled clinical study to demonstrate the safety and efficacy of the applicant's ER formulation (Petition at 1).

FDA is denying the Petition because we do not believe that we treated USL and Supernus disparately. For confidentiality reasons, however, in our response to the Petition we were not able to discuss in detail Supernus's application, including the Agency's reasoning for accepting for filing and tentatively approving the application in the absence of a clinical efficacy study. This confidential memorandum supplements our response to the Petition.

1. **FDA concludes that USL and Supernus were treated similarly; thus there is no reason to delay action on or deny approval of Supernus's application.**

Both applicants were given the same opportunity to justify approval on the basis of pharmacokinetic (PK) data. Both were informed that the Division of Neurology Products (Division) was concerned that traditional PK measures (Cmax, AUC) might not provide reliable evidence of therapeutic equivalence because drugs that were bioequivalent with respect to those measures might nevertheless have differences in the shapes of the blood level curves and those differences could affect pharmacodynamics (PD), i.e., how the drug behaves in the body. This could be significant if the clinical effect of the drug was related to changes in blood levels, if, for example, a clinical effect was caused by a rapid increase in blood levels that would occur after

each administration of the immediate release (IR) product but that would not exist when the ER product was administered.

USL argued that differences in blood level curves did not matter with regard to clinical efficacy. Because USL was unable to present evidence that supported its position, the Division was not convinced that USL had demonstrated that differences in the curves were irrelevant. Supernus addressed the same issue differently. Instead of arguing that differences in blood level curves do not matter, it showed that there is no significant difference in blood level curves between its ER product and the IR drug. If there are no significant differences in blood level curves, then the concern that such differences could result in differences in safety or effectiveness no longer applies.

2. FDA concludes that tentative approval of the Supernus NDA without a clinical efficacy study is justified.

With respect to approval of ER formulations of IR anti-epileptics, it has been the Division's policy to require sponsors to submit either: (1) additional information about the relationship between the ER product's PK profile and PD to show that the shape of the blood concentration versus time curve does not have an impact on clinical efficacy; *or* (2) data from an adequate and well controlled clinical trial demonstrating the efficacy of the ER formulation. FDA treated both USL and Supernus similarly by providing both with the opportunity to provide the information described in (1), which would obviate the need for a clinical efficacy trial.

In its submissions to the Agency, Supernus took advantage of this opportunity to make a compelling scientific argument that a clinical efficacy trial was not needed (Supernus Sn-010 submission, dated January 8, 2010). The principal issue that resulted in the Division's acceptance of Supernus's NDA for filing, and today's tentative approval of Supernus's product on the basis of PK data without a clinical efficacy trial, was Supernus's novel comparison of the blood levels of IR topiramate and Trokendi XR (Supernus's proposed ER formulation of topiramate). Supernus demonstrated that when the blood concentrations and cumulative AUC of Trokendi XR were compared to those of IR topiramate at multiple points in time over a 24 hour period, Trokendi XR fell within the standard bioequivalence range for IR topiramate at almost all points measured.

This point-to-point bioequivalence analysis was crucial to the Division's acceptance of Supernus's argument that a clinical efficacy trial was not needed. Because Supernus met standard bioequivalence criteria (Cmax and AUC within a defined range) *and* demonstrated similar criteria of equivalence at multiple time points over a 24-hour period, the Division concluded that the shape of the Trokendi XR and IR topiramate curves were likely to be "nearly identical." Given that the two curves were so similar, the Division further concluded that there likely would be no pharmacodynamic differences between the two products, and thus a clinical efficacy trial was unnecessary.

Supernus's argument and the Agency's review of Supernus's point-to-point PK comparisons are further explained and discussed in the clinical pharmacology and clinical team leader reviews of the Supernus NDA (see Clinical Team Leader Review of NDA 201-635, June 25, 2012, Norman Hershkowitz, MD, Ph.D.; Clinical Pharmacology Review of NDA 201-635, May 18, 2012, Ta-Chen Wu, Ph.D.).

3. Conclusion

FDA uses its expertise to evaluate the scientific data and regulatory arguments presented by all applicants. For the reasons discussed above and in the NDA review materials, FDA finds that Supernus presented a novel and compelling scientific argument supporting approval of Trokendi XR on the basis of PK data without a clinical efficacy trial. Accordingly, the Agency is tentatively approving the Supernus NDA 201-635 without data from a clinical efficacy study. This tentative approval may be reconsidered if the Agency becomes aware of additional information relevant to approval before the date of final approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
06/25/2012

MEMORANDUM

DATE: June 21, 2012

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 201635

SUBJECT: Action Memo for NDA 201635, for the use of Trokendi XR (topiramate) Extended-Release Capsules as adjunctive and monotherapy of partial and generalized tonic-clonic seizures and the seizures of Lennox-Gastaut syndrome

NDA 201635, for the use of Trokendi XR (topiramate) Extended-Release Capsules as adjunctive and monotherapy of partial and generalized tonic-clonic seizures, and the seizures of Lennox-Gastaut syndrome, was submitted by Supernus Pharmaceuticals, Inc., on 1/13/11. The division refused to file that submission, primarily due to chemistry and manufacturing controls (CMC) deficiencies, clinical pharmacology deficiencies, and the absence of an adequate pediatric development plan. The application was subsequently re-submitted on 8/30/11, and was filed.

This application was filed under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, referencing the Topamax (topiramate) Tablets and Topamax Sprinkle Capsules applications (NDAs 20505 and 20844, respectively). Topamax Tablets and Sprinkle Capsules are approved as:

1) Monotherapy and adjunctive therapy for partial and generalized tonic-clonic seizures in patients 2 years old and older
2) Adjunctive therapy in patients 2 years old and older with seizures associated with Lennox-Gastaut syndrome
3) Prophylaxis of migraine in adults

Supernus is proposing that Trokendi XR be approved as adjunctive and monotherapy for partial and generalized tonic-clonic seizures and the seizures of Lennox-Gastaut syndrome in patients (b) (4) they are not seeking the migraine indication.

Trokendi is a controlled release product designed to be given once a day; the current immediate release Topamax products are given twice a day. The sponsor proposes a pharmacokinetic (PK) basis for approval. That is, they have not performed a controlled trial of Trokendi, but instead have performed several pharmacokinetic studies that they assert establish the effectiveness of Trokendi XR.

The application has been reviewed by Dr. Martin Rusinowitz, medical reviewer, Dr. Norman Hershkowitz, neurology team leader, Dr. Julie Neshiewat, Division of Medication Error Prevention and Analysis (DMEPA), Shawna Hutchins, Division of Medical Policy Programs, Quynh-Van Tran and Sharon Watson, Office of Prescription Drug Promotion, Dr. Eric Brodsky, Study Endpoints and Labeling Development (SEALD), Jeanine Best, Pediatric and Maternal Health Staff, Drs. Ta-Chen Wu and Joo-Yeon Lee, Office of Clinical Pharmacology, Dr. Michael Skelly, Office of Scientific Investigations, Dr. Thomas Wong, Office of New Drug Quality Assessment (ONDQA), Drs. Richard Lostritto, Arzu Selen and Angelica Dorantes, ONDQA, Biopharmaceutics, and Dr. Angela Men, Office of Clinical Pharmacology team leader and Cross-Discipline Team Leader (CDTL). The review team recommends that the application be approved. I will briefly review the relevant data submitted by the sponsor to support approval, and offer the rationale for the division's decision.

It has been the division's position to offer sponsors two approaches to gain approval for a controlled release product when an immediate release product for the same moiety is approved. Because controlled release products typically have substantially different kinetics than the immediate release product, we are concerned that the differences in important pharmacokinetic parameters (e.g., AUC, Cmax, Cmin, Tmax) may result in differences in effectiveness (and perhaps safety). For this reason, we inform sponsors that they must either: 1) perform a controlled clinical trial to establish effectiveness of the controlled release product, or 2) present a compelling argument that the differences in kinetic parameters between the controlled release and immediate release products will not result in a loss of effectiveness known to be provided by the immediate release product. The latter argument may include information relating plasma levels and effectiveness, or other approaches. Unfortunately, however, for most conditions dealt with in our division, we do not have an adequate understanding of the relationship between the shape of the plasma concentration-time curve and effectiveness, typically making the second option unsuccessful. For this reason, in almost all cases, sponsors must perform a controlled trial of the controlled release product to establish effectiveness. In the recent past, for example, controlled release versions of the anti-epilepsy drugs (AEDs) lamotrigine and levatiracetam were approved based on the results of controlled trials.

This policy was discussed with Supernus on several occasions during the development of this drug. Ultimately, they decided to pursue the second approach. That is, they have submitted pharmacokinetic data that they believe establish the effectiveness of their controlled release product. The study that serves as the primary basis of this approach was a pharmacokinetic study performed in healthy volunteers. I will briefly describe this study.

Study 103 was a cross-over study in healthy volunteers comparing Trokendi XR 200 mg once a day to Topamax Tablets 200 mg/day (given as 100 mg BID). In each period, patients received the following treatment on the following days:

Days 1-7: 50 mg/day
Days 8-14: 100 mg/day
Days 15-21: 150 mg/day
Days 22-31: 200 mg/day

On Day 31 of each period, plasma levels were assessed at numerous time points. A total of 33 subjects had plasma levels drawn in both periods.

The 90% Confidence Intervals for the ratio of Cmax, Cmin, and AUC 0-24 for Trokendi XR and Topamax all met standard bioequivalence standards (that is, the 90% CIs fell within .80-1.25). Tmax for Topamax was 1 hour, and Tmax for Trokendi XR was 6 hours.

However, in addition to these standard metrics, the sponsor performed two additional analyses.

First, they compared partial AUCs for the two products. These partial AUCs were calculated as follows:

AUC 0-.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24

The 90% CIs for the ratios of all of these partial AUCs fall within .80-1.25.

The sponsor also compared the ratios of the following partial AUCs from t1-t2 as follows:

AUC 0.5-1; AUC 1-1.5; AUC 1.5-2; AUC 2-3; AUC 3-4; AUC 4-6; AUC 6-8; AUC 8-12; AUC 12-16; AUC 16-24. The 90% CI for all of these ratios fell within .8-1.25 except for the following lower limits:

	Lower limit of 90% CI
AUC .5-1	77
AUC 1-1.5	78

Topiramate concentrations were obtained at all of these time points as well.

The 90% CIs for the ratios of the plasma levels ***at all of these time points*** also

fell within .80-1.25 except for the lower limits of the CIs at the following time points:

	Lower limit of 90% CI
$C_{0.5}$	78
C_1	77
$C_{1.5}$	79

The sponsor performed another PK study, Study 108 in which patients on a stable dose of immediate release Topamax (200, 250, 300, 350, or 400 mg/day) were switched to the same daily dose of Trokendi XR. Pharmacokinetic parameters were compared after two weeks of each treatment.

The 90% CIs for the ratios of AUC 0-24, Cmax, and Cmin of Trokendi XR (N=60) and Topamax (N=59) all fell within .8-1.25. A total of 95 patients (N=48, Topamax; N=47 Trokendi XR) were taking non-enzyme inducing AEDs. AUC, Cmax, and Cmin met bioequivalence standards for these patients.

A total of 24 patients (N=11, Topamax; N=13 Trokendi XR) were receiving enzyme-inducing AEDs. In these patients, the lower limits of the 90% CIs for the ratios of Cmax and Cmin were 79 and 74, respectively. The geometric LS mean ratios for Trokendi XR/Topamax for Cmax and Cmin were 96 and 90, respectively, in these patients.

The sponsor also offered several other arguments to support their view that the characterization of the pharmacokinetics of their product is sufficient to establish the effectiveness of Trokendi XR, and that, therefore, a controlled trial is unnecessary. These arguments include an argument related to what they believe to be the range of plasma levels of topiramate that confer effectiveness, a decreased fluctuation index of the XR compared to immediate release topiramate, and similar plasma levels in patients and healthy volunteers.

There are no safety issues of concern, with one exception.

It is Agency policy that controlled release products must be subjected to an in vitro test of the interaction with alcohol, to determine if such products release the active moiety excessively rapidly under these conditions. If a significant “dose dumping” effect is seen in vitro, the sponsor must perform an in vivo test to examine if this phenomenon will be clinically significant.

Supernus performed the required in vitro test, and documented a very significant effect of alcohol on dissolution of the product. Specifically, there was an increase in the rapidity of dissolution at 20% (v/v) alcohol, but a highly significant increase at 40% (v/v). In effect, by 30 minutes, (b) (4) of the topiramate was released in 40% alcohol. By comparison, the proposed dissolution specifications require that no more than about (b) (4) (depending upon dose) be released by 4 hours, and that (b) (4) (or greater) be released by 8 hours.

In order to further address this issue, the sponsor performed an in vivo study in dogs (up to 40% alcohol). Although the results demonstrated no significant effect, the division has on multiple occasions during the development of this product informed the sponsor that the dog study was unacceptable, and that a study in humans must be performed. Clearly, the in vitro results may have profound clinical importance if Trokendi XR were to be taken with alcohol, and the division believes that a definitive human study must be performed in order to characterize if such an interaction will occur in people, and, if so, how significant it would be.

As noted above, the sponsor has proposed that Trokendi XR be approved for patients (b) (4)

With regard to the question of the (b) (4) age limit that could be included in labeling, a few comments are needed.

(b) (4)

Further, there have been extensive internal discussions about the ability of (b) (4) to swallow intact the capsule sizes proposed for Trokendi XR. There has been general agreement that patients below the age of 6 years could not easily, or safely, swallow the capsules that would be necessary to provide the appropriate dose. For this reason, the youngest patients for whom Trokendi XR could be approved is 6 years old.

COMMENTS

As noted above, Supernus has proposed that Trokendi XR be approved as a treatment for epilepsy based, primarily, on the results of Study 103, a study in healthy volunteers that compares plasma topiramate levels at steady state on Topamax 100 mg BID and Trokendi XR 200 mg once a day.

In this study, the sponsor has shown, not only that Trokendi XR meets the Agency's bioequivalence standard for Cmax, Cmin, and AUC, but also that these bioequivalence standards are met for the comparison of plasma levels at multiple

time points during 24 hours, as well as for multiple partial AUCs from time zero, and for partial AUCs for multiple contiguous time points. This approach to demonstrating similarity of plasma concentration-time curves between an immediate release and a controlled release dosage form appears to be unprecedented; there is no record of a similar approach having been previously taken by a sponsor, either in the Office of New Drugs or in the Office of Generic Drugs.

As described earlier, the division offers sponsors of controlled release products the option of demonstrating that differences in the shapes of the concentration-time curves between controlled release and immediate release products are irrelevant with regard to effectiveness, in lieu of having to perform a randomized controlled trial to demonstrate that the controlled release formulation is effective. In all recent previous cases, however, we have not been convinced that we have sufficient information about the relationship between the shape of these curves and effectiveness to conclude that the differences are clinical inconsequential. For this reason, recent previous sponsors of controlled release AEDs (Lamictal and Keppra) have performed controlled trials that served as the basis for the determination of effectiveness. (Indeed, as of this writing, the sponsor of another controlled release topiramate product is performing a controlled trial. That sponsor offered an argument based on PK, in an attempt to have their drug approved without having to perform a controlled trial. We did not find that particular argument persuasive. As a result, they have filed a Citizen's Petition arguing that all sponsors of controlled release AEDs must be required to perform a controlled trial to demonstrate effectiveness [see my memo to the file that further describes this situation]).

However, given the findings in Study 103, we believe it is reasonable to conclude that Trokendi XR is effective, and that a controlled trial is not necessary to demonstrate effectiveness. We come to this conclusion because the analyses presented by Supernus establish, in our view, that the plasma levels of topiramate achieved during the course of a 24 hour dosing period with Trokendi XR are sufficiently similar to those produced by Topamax given twice a day to conclude that the two products will have similar clinical effects. Although the two curves are not, strictly speaking, "superimposable", the fact that the plasma levels (and corresponding partial AUCs) ***meet established standards for similarity throughout the dosing interval, and not just for Cmax, Cmin, and AUC***, is powerful evidence that the two curves are sufficiently similar to support the conclusion that the two drugs will provide equivalent clinical effects.

As noted earlier, similar analyses have not been performed or submitted by other sponsors of controlled release products, and the PK arguments for not having to perform a controlled trial to establish effectiveness that have been made by other sponsors typically rely, prominently, on the plasma levels achieved with the controlled release product falling in what are believed to be some therapeutic range (though there are also typically other elements to the argument as well).

Supernus has submitted, in addition to its PK data, similar arguments. However, as discussed above, we have not considered these arguments compelling, given the lack of well-documented therapeutic ranges for most drugs, as well as other flaws in typical arguments (for example, many sponsors include as elements to their arguments statements about the mechanism of action, as it relates to plasma levels. Again, we have never found these arguments persuasive, given the lack of detailed information about the mechanism of action in the typical case). In this case, however, Supernus's data and analyses, documenting the similarity of topiramate plasma levels produced by Trokendi XR and Topamax throughout the dosing interval (not just for Cmax, Cmin, and AUC), provide, in our view, a compelling basis for concluding that Trokendi XR will be effective.

With regard to safety, as previously discussed, there are no safety issues associated with the use of Trokendi XR that would preclude approval. However, also as noted earlier, in vitro data document an important effect of alcohol on the dissolution of the product, suggesting that there may be dangerously high levels of topiramate early after drug administration, and possibly sub-therapeutic levels later in the dosing interval.

Although the division repeatedly informed the sponsor that the alcohol interaction study performed in dogs was not an acceptable substitute for the required study in people, the sponsor did not perform a human alcohol interaction study. Because we have no empirical data that addresses how long before or after drug administration alcohol can be safely ingested, we have concluded, based on numerous considerations, that, in order for Trokendi XR to be given safely, alcohol should not be ingested between 6 hours before and 6 hours after drug administration; this will be reflected in product labeling.

One final, and very important, point.

The sponsor of Topamax has performed studies in pediatric patients from 1 month to 2 years old. In this population, the incidence of various adverse reactions (including infections, elevated creatinine, death, and decreased growth parameters) was considerable, and this information has been deemed sufficiently important to be included in the labeling for generic versions of topiramate, despite the fact that no topiramate product is approved for patients in this age range. We believe that this information must be included in the label for Trokendi XR as well (despite the fact that, it too, will not be indicated for this population, and despite the fact that these young patients could not swallow the intact capsule, we believe it may be used in these patients by opening the capsule and sprinkling the contents on food, or administered via an in-dwelling gastric tube).

However, this information is also considered protected information until 2013. And though the Agency is legally permitted to include this safety information in the labeling for generic products (despite the fact that it is still protected), the Agency is not legally permitted to include this pediatric safety information in the

label for a product approved under 505(b)(2) (see the 6/12/12 review by Jeanine Best of the Pediatric and Maternal Health Staff). Therefore, this product cannot be finally approved until the protection for this information has expired.

Therefore, for the reasons given above, I will issue the attached tentative approval letter (with attached labeling) for Trokendi XR for its use in monotherapy for partial onset and primary generalized tonic-clonic seizures in patients 10 years of age and older, for adjunctive therapy for partial and primary generalized tonic-clonic seizures for patients 6 years of age and older, and for adjunctive therapy for seizures associated with Lennox-Gastaut syndrome for patients 6 years of age and older.

Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
06/25/2012

Cross-Discipline Team Leader Review

Date	6/22/2012
From	Angela Yuxin Men., MD PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 201635 Original NDA
Applicant	Supernus Pharmaceuticals, Inc.
Date of Submission	8/30/2011 (Agency received on 9/9/2011)
PDUFA Goal Date	7/9/2012; move to 6/25/2012 due to the Citizen Petition
Proprietary/ Established (USAN) Name	Trokendi XR™
Dosage forms / Strength	Extended Release (ER) Capsules (25mg, 50mg, 100mg, 200mg)
Proposed Indication(s)	Treatment in patients (b) (4) years of age (children and adults) in the following disorders: 1) Partial Onset Seizures (POS) (monotherapy and adjunctive treatment) 2) Primary Generalized Tonic-Clonic (PGTC) Seizures (monotherapy and adjunctive treatment) 3) Seizures Associated with Lennox- Gastaut Syndrome (LGS) (adjunctive treatment)
Recommended:	Tentative Approval

1. Introduction

Trokendi XR™ (topiramate extended-release or ER capsules; SPN-538T) is intended to use as monotherapy and adjunctive therapy for epilepsy via 505(b)(2) application using the approved TOPAMAX® immediate-release (IR) tablets (NDA 20-505) as the reference list drug (RLD). Since Trokendi XR™ is intended to be taken as an intact capsule, the Sponsor is seeking a monotherapy and adjunctive therapy indications for patients with epilepsy (b) (4) The Sponsor is not seeking indication for migraine. Trokendi XR™ capsules are multi-bead capsules (three-pellet composite formulations) in dosage strengths of 25, 50, 100, and 200 mg, administered once daily (QD).

In this submission for Trokendi XR™, the applicant seeks approval by applying a NOVEL bioequivalence (BE)-based method in a PK study, demonstrating the BE at multiple time-points within the 24 hours at steady-state between the proposed Trokendi XR™ capsules given once-daily (QD) and the approved TOPAMAX® IR tablets given twice-daily (BID), without conducting a clinical efficacy trial. (see section 2 for detailed justification). It has been confirmed that the applicant's proposed BE-based method is novel and has not been utilized in the past within Office of Clinical Pharmacology and Office of Generic Drugs for regulatory approval.

2. Regulatory Background

The current submission is a resubmission of the NDA 201-635 that was originally submitted to the Agency on January 14, 2011 but was subject of a refused to file on March 14, 2011 due to the CMC filing issues. The Table below lists the key meetings for this submission.

Original IND by Supernus	September 29, 2008	
EoP2	October 15, 2009	New BA/BE approach proposed
Type C	January 8, 2010	Scientific justifications provided
Pre-NDA	July 28, 2010	
NDA submission	January 14, 2011	Refused to file
NDA re-submission	September 9, 2011	

The applicant seeks approval by applying a new clinical pharmacology-based method, demonstrating the bioequivalence (BE) at multiple time-points within the 24 hours at steady-state between the proposed Trokendi XR™ capsules QD and approved TOPAMAX® IR tablets given twice-daily (BID), without conducting the clinical efficacy trial.

The proposed total daily dose for Tokendi XR™ QD is the same as that for the reference drug TOPAMAX® IR tablets BID, which is supported by the BE with respect to AUCτ, Cmax, Cmin, and point-to-point comparison for topiramate partial AUC (AUC0-p; 'p' represents time points post-dose) at steady-state. Additional analyses showed that the point-to-point comparisons for topiramate plasma concentrations and the partial AUC between time-points (AUCt1-t2) are BE at steady-state for most of the time points throughout the day based on conventional BE criteria, except for the initial time points, mostly before 1.5 hour postdose. Given known efficacy and safety profiles for TOPAMAX IR, as well as the supportive evidence listed below, the applicant's novel BE-based approach is considered reasonable.

- Reported therapeutic window for topiramate
  - Unbound topirmate plasma concentrations closely reflect the concentrations in the cerebrospinal fluid, and hence represent a reasonable surrogate for assessing topiramate concentrations in CNS (*Christensen et al. Ther Drug Monit. 2001 Oct;23(5):529-35*).
  - The median percent reduction and percent responders were the greatest in the mid-range plasma topiramate concentrations from 3.2 to 5.4 μg/mL (*TOPAMAX® sNDA, 1998*).
  - In a published concentration-controlled clinical study, the authors concluded that the "optimal treatment response is most likely found between 2 mg/L and 10.5 mg/L." (*Christensen et al. Neurology. 2003 Nov 11;61(9):1210-8*)
  - In pooled dose-response studies in adults with partial onset seizures (400, 600, 800, or 1000 mg/day, with doses ≥600 mg/day yielded Cmin proportionally higher than 10 mg/L), the author reported no significant improvement in

efficacy at doses >400mg/day (*Peeters et al. Acta Neurol Scand. 2003;108:9-15*).

- Relatively small magnitude of fluctuation compared with ER formulations of other approved AEDs
- Relative small intra- and inter-subject variability
- Switchability from TOPAMAX IR to Trokendi XR™ in epilepsy patients
- A similar exposure-response relationship for efficacy was established between steady-state topiramate trough concentration (Cmin) and percent reduction in seizure frequency for the IR formulations between adults (16 years and above) and pediatrics (6-15 years) (refer to Dr. Anshu Marathe's review for NDA 20505/S042, 20844/S036, 7/11/2011 in DARRTS).

The following are the key primary reviewers for the Trokendi XR™ NDA:

- Clinical: Martin Rusinowitz, MD.
- Clinical Pharmacology: Ta-chen Wu, Ph.D.
- Pharmacometrics: Joo-Yeon Lee, Ph.D.
- CMC: Thomas Wong, Ph.D.
- Biopharmaceutics: Arzu Selen, Ph.D., Angelica Dorantes, Ph.D., Richard, Lostritto, Ph.D.

3. CMC

From a CMC perspective, the sponsor has submitted sufficient and appropriate information to support the approval of the drug products, Topiramate Extended-Release Capsules. There is no post-approval agreement.

4. Nonclinical Pharmacology/Toxicology

NA.

5. Biopharmaceutics

The highlights of biopharmaceutics review are the followings:

1) Based on in vitro and in vivo assessments, there is adequate information to support bioequivalence of the 25 mg capsules, at equimolar dose, to the higher strengths (also manufactured at commercial scale) and the biowaiver request for the 25 mg capsules is acceptable.

2) Dose dumping effect was observed in the in-vitro alcohol test.
In vitro data show that, in the presence of alcohol, the pattern of topiramate release from Trokendi XR™ capsules is significantly altered. Although at the pre NDA meeting and other

meetings, a clinical alcohol dose dumping study Trokendi XR™ was requested from the Agency, the Applicant has not responded. Instead, an in vivo study in dogs was conducted to evaluate the potential dose-dumping with alcohol (0%, 10%, and 40%). However, the dog was never shown to be a suitable in vivo predictive model for potential dosage form and alcohol interaction in humans.
Based on the *in vitro* data, in the presence of alcohol, plasma levels of topiramate with Trokendi XR™ may be markedly higher soon after dosing and subtherapeutic later in the day. Topiramate is a CNS depressant. Concomitant administration of topiramate with alcohol can result in significant CNS depression. And the altered pattern of topiramate release from Trokendi XR™ capsules with alcohol may increase the likelihood of breakthrough seizures.
As there is no in-vivo results regarding the effect of alcohol on Trokendi XR™ in humans, per the current available information on the kinetics of alcohol, variability of GI emptying time and other confounding factors (e.g., meal etc.), restriction for the alcohol consumption 6 hours prior and after administration of Trokendi XR™ dosing is recommended by the Agency for the labeling (Contraindication and Warnings and Precautions sections).

3) In terms of in-vitro dissolution performance, the drug product exhibits larger variability between batches comparing within a given batch. For Trokendi XR™, specifically for the three hour time point, between batch variability resulted in a proposed dissolution range of approximately the mean (of multiple batches at this time point) + 15%, which is out of the range of + 10% about the mean we considered a good quality product. The applicant explained that the source of the variability appears to involve the functional release coating (b) (4) which the applicant was more recently learning to control. However, this control was **NOT** implemented in the stability studies submitted to the NDA.

As topiramate is not new to the United States market, based on the known safety and efficacy profile, there was no obvious risk which would preclude allowing the + 15% window for dissolution at the three hour time point. Thus, from the ONDQA-Biopharm primary review perspective, the + 15% window at the three hour dissolution time point was also a reasonable and acceptable risk in terms of safety and efficacy. However, there is a concern over this lack of robustness of dissolution performance based on the NDA stability batch performance.

Per the communication with the Applicant during the review cycle, data provided by the applicant indicate that recent improvements in the control of the excipient (b) (4) will reduce between batch variability to a level normally associated with a good quality drug product of this type (e.g., + 10%). Therefore, ONDQA-Biopharm recommends that the applicant's proposed dissolution criteria be accepted as amended via their recent agreement to the Q (b) (4) at six (6) hour condition. However, as part of this recommendation, the applicant will be asked to agree to provide appropriate data within fourteen (14) months of approval (via the appropriate submission pathway) which either support the current specification or provide the basis to tighten the 3 hour dissolution limit to (b) (4) about the mean.

The following comments were sent to the applicant on June 14, 2012.
1. Your proposal of setting the dissolution acceptance criteria for your product on an interim basis for one year is acceptable. Please provide the updated specification Table for your product with the revised dissolution criteria.

2. Additionally, we remained most concerned regarding the three (3) hour time-point dissolution limits which appear to be set wide based on between batch variability. We the dissolution data between batches and that you have implemented a corrective action which is expected to minimize between batch variability in commercial manufacturing. Therefore, for the setting of the final dissolution acceptance criteria, we request that you agree to the following:

   - To collect additional dissolution profile data for the commercial validation batches (each strength) manufactured during the first year after the action date, targeting more appropriate acceptance criteria in alignment with the FDA standards described in IVIVC-Guidance Section B-1 (Setting Dissolution Specifications without an IVIVC).
   - To use the additional dissolution data generated from the commercial validation batches for the setting of the final acceptance criteria.
   - To submit a prior approval supplement to the NDA within 14 months from the action date, including a proposal for the final acceptance criteria and the supportive dissolution data (each strength) from the commercial validation batches which are based on and reflective of the data discussed herein.

On June 19, 2012, a teleconference was held between the Applicant and ONDQA review team. Please refer to the Memo of this meeting in DARRTS dated June 22, 2012 for an agreement being sought.

6. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) 1 has reviewed the submission and finds NDA 201-635 acceptable from an OCP perspective.

Linear pharmacokinetics of topiramate from Trokendi XR™ was observed following a single oral dose over the range of 50 mg to 200mg. The peak plasma concentrations (Cmax) of topiramate occurred at approximately 24 hours following a single 200 mg oral dose of Trokendi XR™. The mean elimination half-life of topiramate was approximately 31 hours following repeat administration of Trokendi XR™. Trokendi XR™ can be taken without regard to meals.

In this 505(b)(2) application for Trokendi XR™, the central piece is that the applicant seeks approval by applying a NOVEL bioequivalence (BE)-based method in a PK study, demonstrating the BE at multiple time-points within the 24 hours at steady-state between the proposed Trokendi XR™ capsules given once-daily (QD) and the approved TOPAMAX® IR tablets given twice-daily (BID), without conducting a clinical efficacy trial. In this submission, relative Bioavailability of Trokendi XR™ Compared to Immediate-Release Topiramate studies were conducted in both healthy volunteers and in patients with epilepsy.

Study in Healthy Normal Volunteers (Study 538P103)

Trokendi XR™ taken once a day provides steady state plasma levels comparable to immediate-release topiramate taken every 12 hours, when administered at the same total 200

mg daily dose. In a crossover study, 33 healthy subjects were titrated to a 200mg dose of either Trokendi XR™ or immediate-release topiramate and were maintained at 200mg per day for 10 days.

The 90% CI for the ratios of AUC_{0-24}, C_{max} and C_{min}, as well as partial AUC (the area under the concentration-time curve from time 0 to time p (post dose) for multiple time points were within the 80 to 125% bioequivalence limits, indicating no clinically significant difference between the two formulations. In addition, the 90% CI for the ratios of topiramate plasma concentration at each of multiple time points over 24 hours for the two formulations were within the 80 to 125% bioequivalence limits, except for the initial time points before 1.5 hour post-dose.

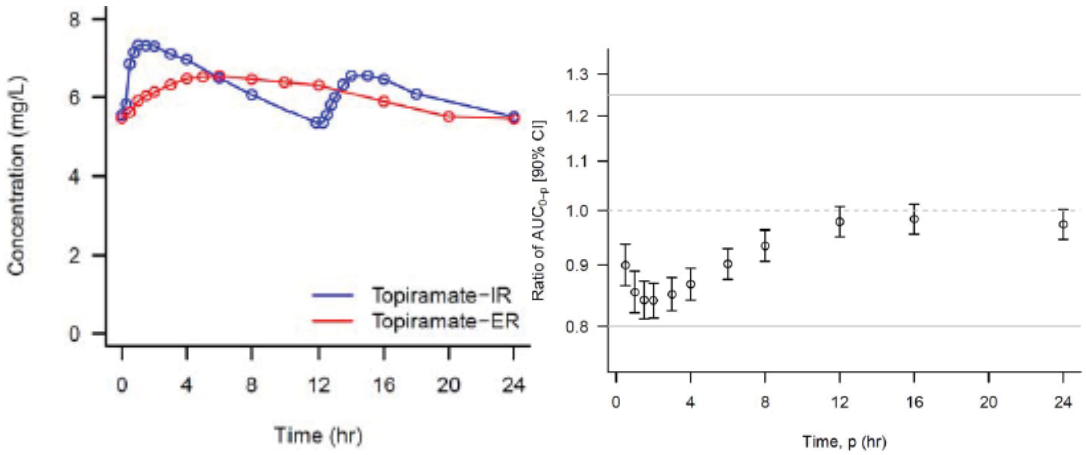
Values for key pharmacokinetic parameters (AUC, C_{max} and C_{min}) and for the Fluctuation Index (FL) are shown in the following Table:

Steady State Bioavailability of Trokendi XR™ Compared to Immediate-release Topiramate in Healthy Volunteers

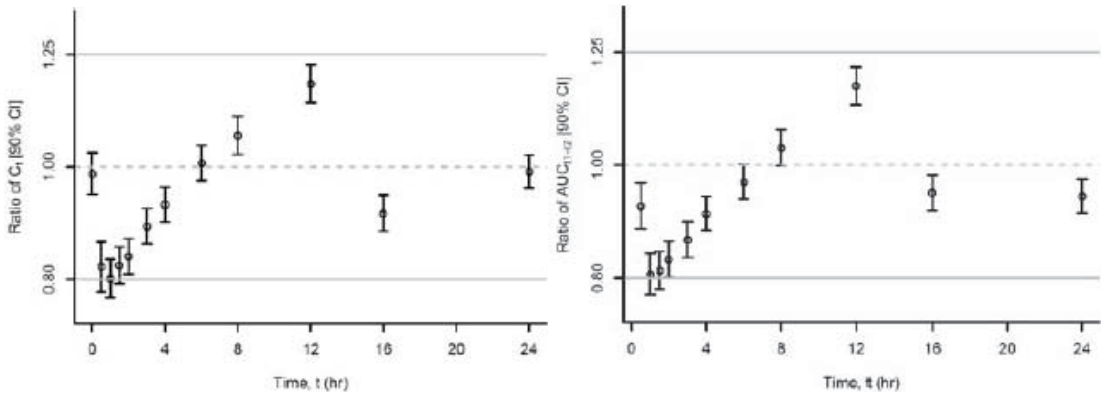
Parameter	Immediate-Release Topiramate (n = 33) Geometric Mean	TRADENAME (n = 33) Geometric Mean	Ratio (%) / Difference	90% CI
AUC (hr•mg/L)	149	144	97.1	(94.01, 100.21)
C_{max} (mg/L)	7.60	6.69	88.0	(85.10, 91.02)
C_{min} (mg/L)	5.13	5.12	99.9	(95.87, 104.13)
FL (%)	40.1	26.1	-14.1*	(-16.68, -11.49)

* Comparison of FL $[(C_{max}-C_{min})/C_{avg}]$ is presented as a difference, not a ratio.

The left figure presented below shows concentration versus time profiles for immediate-release topiramate and Trokendi XR™ at steady state in healthy subjects.
The right figure showed established BE of point-to-point comparison for (XR/IR) ratios of partial AUC (AUC0-p, ('p' represents time points post-dose)) at steady-state (i.e., at all time-points throughout the day), suggesting the profile similarity



In addition, BE established for point-to-point comparison for topiramate plasma concentrations (Left Figure) and ratios of partial AUC (AUCt1-t2) (Right Figure) at steady-state (except for the initial time-points)



Study in Patients with Epilepsy (*Study 538P108)*

In a study in epilepsy patients treated with immediate-release topiramate alone or in combination with either enzyme-inducing or neutral AEDs who were switched to an equivalent daily dose of Trokendi XR™, there was a 10% decrease in AUC_{0-24}, C_{max}, and C_{min} on the first day after the switch in all patients. At steady state, AUC_{0-24} and C_{max} were comparable to immediate-release topiramate in all patients. While patients treated with Trokendi XR™ alone or in combination with neutral AEDs showed comparable C_{min} at steady state, patients treated with enzyme-inducers showed a 10% decrease in C_{min}. This difference is likely not clinically significant and probably due to the small number of patients on enzyme-inducers. The Table below summarized these key PK parameters obtained from this study.

Summary of Bioequivalence (ANOVA) Results at Steady State for Primary Endpoints (Day 28 vs Day 14) – Pharmacokinetic Population

Population	N	C_{max}			C_{min}			AUC_{0-24}		
		Ratio	Lower 90%	Upper 90%	Ratio	Lower 90%	Upper 90%	Ratio	Lower 90%	Upper 90%
All (PK)	62	0.95	0.82	1.10	0.97	0.80	1.18	0.99	0.84	1.16
Neutral	49	0.98	0.86	1.12	1.03	0.89	1.18	1.02	0.90	1.16
Induced	13	0.96	0.79	1.17	0.90	0.74	1.09	1.02	0.85	1.23

Based on reported therapeutic window and the known exposure-response information, the overall results suggested that patients can be switched from taking topiramate IR to Trokendi XR™ of the same total daily doses.

In summary, the applicant had demonstrated the BE between the proposed Trokendi XR™ capsules given once-daily (QD) and the approved TOPAMAX® IR tablets given twice-daily (BID) using the NOVEL bioequivalence (BE)-based method.
OCP believes that this provides reasonable justification to conclude that the shape of the curves do not significantly differ between the proposed Trokendi XR™ capsules given once-daily (QD) and the approved TOPAMAX® IR tablets given twice-daily (BID) and thus pharmacodynamic equivalence can be concluded without conducting a clinical efficacy trial.

7. Efficacy

There is no clinical efficacy trial conducted.

8. Safety

As noted above, this approval is based upon a demonstration of PK equivalency of Trokendi XR™ to the referenced label drug, TOPAMAX® IR. This should apply to both issues of safety as well as efficacy conclusion. The safety of this drug is therefore largely based upon the safety of the referenced label drug, TOPAMAX® IR.

Although there is no specific efficacy/safety study conducted, safety data were collected from the Trokendi XR™ Clinical Pharmacology studies from a total of 320 normal healthy subjects and 62 epilepsy patients enrolled. The Medical Officer examined these safety data and the limited empirical data do not indicate any significant difference in the safety profile between TOPAMAX® IR and Trokendi XR™. This is further supported by the extensive demonstration of the equivalence between the shapes of time/concentration curves indicating a pharmacodynamic equivalence.

9. Advisory Committee Meeting

None

10. Pediatrics

The referenced label drug, TOPAMAX® IR, which is available as both tablet and sprinkle capsules, is indicated for POS and PGTC seizures as both monotherapy and adjunctive therapy down to 2 years of age, and adjunctive treatment for seizures of LGS down to 2 years of age. In the present NDA, the Sponsor is requesting all indications (b) (4) The basis of the Sponsor's request is that the developed capsules could not be swallowed in patients (b) (4) because of their size.

This Division met with the PERC Committee on 5/23/12 and agreed with the following principals to guide drug labeling and PREA requirement:

- Although the Applicant contends that the capsule can be swallowed whole (b) (4) there was consensus at the committee that, because of the size of such capsules, that it was unsafe to label the medication below 6 years old.
- Although the capsule can be opened, and a bioavailability study indicated that there is bioequivalence when mixed in applesauce, it was determined that because the slow release nature of this formulation is dependent on the intact medication particles and that chewing can undermine this process, the medication could not be labeled for sprinkle use. The Applicant was asked, in a previous communications, to developed a pediatric friendly formulation (e.g. a liquid formulation), or, prove, that due diligence was taken to developed such a formulation without success. The Applicant has yet to provide this Division with such convincing requested information.

- Topamax use as monotherapy in children less then ages of 10 years old, for POS and PGTC seizures is still on patent protection, and cannot the labeled.

This has led to an agreement for the following pediatric indications:

- Partial Onset Seizure and Primary Generalized Tonic-Clonic Seizures:
  - Initial monotherapy in patients 10 years of age and older
  - Adjunctive therapy in patients 6 years of age and older.
- Adjunctive treatment in seizures associated with LGS in patients 6 years and older.

The following PREA issues/requirement were identified:

- The Applicant should develop a child friendly XR formulation (e.g. liquid), with similar pharmacokinetic properties as Trokendi XR™. If this is not possible they must demonstrate, with due diligence, that such an attempt was made.
- The following are waived because an insufficient patients with the disorder an be identified and the consequent impracticality in performing such studies:
  - Adjunctive POS treatment in patients less then 1 month of age
  - Adjunctive PGTC seizure treatment patients less then 2 years of age.
- The following are deferred, to allow the Applicant to develop a child friendly XR formulation (e.g. liquid), with similar properties as that demonstrated for Trokendi XR™ (if this is not possible they must demonstrate, with due diligence, that such an attempt was made:
  - Adjunctive POS pharmacokinetic, efficacy and safety treatment study in patients 1 month to 6 years.
  - Adjunctive PGTC seizure pharmacokinetic, efficacy and safety treatment study in patients 2 years to 6 years.
- The following are waived because such studies are considered unethical[1]:
  - Monotherapy studies in POS in patients 1 month to 6 years old
  - Monotherapy studies in PGTC seizures in patients 2 years to 6 years old.
- Seizures resulting form LGS is not considered a PREA issue as it is an orphan indication.

There is patent protected information for the safety outcomes obtained from a 1 to 24 month children study in the proprietary label. During a generic carve out review, this information was deemed crucial for the safe use of this product, and was therefore not removed from the generic label. As the Division has been advised that there is no legal authority allowing the maintenance of such information in a 505(b)(2) applications, a tentative approval must be granted till this patent expires on June 22, 2013 (http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=020844&Product_No=001&table1=OB_Rx).

[1] Note: The epilepsy community considers placebo control studies as unethical. While the Division is presently allowing for historical controls trial in adults based upon well document historical control data, no such data exists for children, therefore such studies cannot be performed. If the new formulation, however, exhibits the same properties as that of the present formulation, this reviewer believes that a monotherapy indication may be possible.

Also of note the monotherapy indication for POS and PGTC seizures in the 2 to 10 year age group has patent protection. But, it is believed that this can be removed from the label without affecting this drugs safe use.

11. Other Relevant Regulatory Issues

- *Exclusivity or patent issues of concern*

There is patent protected information in the topiramate IR label regarding safety outcomes in a 1 to 24 month study in children (Section 10). As the Division has been advised that there is no legal authority allowing the maintenance of such information in a 505(b)(2) application, a **tentative approval** must be granted till this patent expires on June 22, 2013 (http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=020844&Product_No=001&table1=OB_Rx).

- *Citizen Petition*

The Agency received a Citizen Petition submitted on December 28, 2011 by Upsher-Smith Laboratories (USL or Petitioner). The response to this Citizen Petition is due on June 25, 2012. In order to release the review decision for this NDA201635 at the same time with the response to this Citizen Petition, the original PDUFA date, July 9, 2012, was revised to June 25, 2012.

Same as Trokendi XR™ Supernus developed, USL is also seeking approval of an extended release (ER) version of topiramate. The Petition alleges that because the Agency requested that USL conduct a clinical efficacy study to support approval of its 505(b)(2) NDA for ER topiramate, it would be "inequitable and inconsistent" to approve another sponsor's application for ER topiramate without such a study. The Petitioner specifically argues that if FDA were to approve Supernus's 505(b)(2) NDA for ER topiramate without data from a clinical efficacy study, this would constitute disparate treatment of similarly situated parties in violation of the Administrative Procedure Act (APA).

Per the information summarized in this memo and the previous communications with USL, FDA concludes that USL and Supernus were treated similarly; thus there is no reason to delay action on or deny approval of Supernus's application. FDA also concludes that tentative approval of the Supernus NDA without a clinical efficacy study is justified.

- OSI inspections for clinical pharmacology Studies 539P103, 538P106-200, 538P106, 538P106-50 did not raise issues of concern for approvability.
- DMEPA found the proprietary name, Trokendi XR™, acceptable.

12. Labeling

See labeling included in the Divisions action letter.

13. Recommended Regulatory Action

The Sponsor's submission provides adequate information for regulatory approval of Trokendi XR™. However, the tentative approval action will have to be taken because of pediatric issues discussed Section 10.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUXIN MEN
06/22/2012

MEHUL U MEHTA
06/22/2012

Team Leader Review

Date	6/15/12
From	Norman Hershkowitz, MD, PhD
Subject	Clinical Team Leader Review
NDA/BLA # Supplement#	201635
Applicant	Supernus Pharmaceuticals, Inc.
Date of Submission	8/30/11
PDUFA Goal Date	7/9/12
Proprietary Name / Established (USAN) names	Topiramate XR/ Trokendi XR
Dosage forms / Strength	Capsules/ 25, 50, 100, and 200 mg
Proposed Indication(s)	Treatment in patients (b) (4) (children and adults) in the following disorders: 1. Partial Onset Seizures (monotherapy and adjunctive treatment) 2. Primary Generalized Tonic-Clonic Seizures (monotherapy and adjunctive treatment) 3. Seizures Associated with Lennox- Gastaut Syndrome (adjunctive treatment)
Recommended:	Tentative Approval (b) (4)

1. Introduction

Trokendi XR is an extended release formulation of the referenced label drug Topamax (topiramate) that is designed to be used once daily. Topamax is labeled for twice daily use. Topamax was originally approved in 1996 with later efficacy supplements for different indications and populations. Topamax is presently approved for monotherapy and adjunctive therapy for seizures classified as partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) in patients older 2 years and above as well as adjunctive treatment in patients with seizures associate with Lennox-Gastaut syndrome (LGS) in patients 2 years and above. It is also indicated as migraine prophylaxis in adults. The Sponsor is asking for the same seizure indication for Trokendi XR, with the exception that they are asking that it only be labeled for patients (b) (4)

2. Background

This formulation was originally submitted as an IND on 9/29/11. In response to the Sponsor's request for a Type C meeting (4/16/08), the Division, in a communication dated 6/6/08, informed the Sponsor that it is usually not the policy of the Division to approve such applications based solely on PK data, because of concern that although traditional

bioequivalence standards during maintenance may be fulfilled, the shape of the curves (e.g. slopes) may differ, and that it is unknown how this difference will effect pharmacodynamic properties of the drug (e.g. efficacy). However, as is routinely noted at such meetings, the Division informed the Sponsor that they may provide a cogent argument as to why approval could be based solely on PK and without a formal adequately controlled safety and efficacy study. In a latter submission (11/13/09) the Sponsor presented additional information including traditional bioequivalence data (Cmax, Cmin and AUC) as well as an analysis at multiple time points of point concentrations and cumulative (partial) AUCs. Nonetheless, the Division responded by noting that we were not convinced that this would allow us to waive the requirement of a traditional adequately controlled efficacy/safety study, as this did not prove that shapes of the curves were equivalent. In a later type C meeting (2/8/10), the Sponsor presented an argument for approval without a traditional efficacy trial. The principal aspect of the Sponsor's argument was that not only did the PK study demonstrate that it fulfilled traditional bioequivalence standards, but that examination of multiple time points of concentrations and cumulative AUCs over a 24 hour period at steady state maintenance, when analyzed, met standard bioequivalence standards for confidence intervals. Because this appeared to indicate that there may be little difference between the actual shapes of the curves, the division responded in a communication dated 2/5/10 that we would be willing to file the application without an efficacy study.

The NDA was submitted on 1/14/11 as a 505(b)(2) NDA, but a refuse to file decision was issued because of CMC issues. This was corrected and the application was finally resubmitted on 8/30/11 and subsequently filed.

3. CMC/Device

No issues have been identified. The reader is referred to the CMC and ONDQA for details.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Biopharmaceutics

A principal issue in the OCP reviewed is that of pharmacokinetic/pharmacodynamic similarity to Topamax. For this issue the reader is referred to Section 7, Clinical/Statistical Efficacy. The OCP reviewers (primary reviewer Dr. Ta-Chen Wu and Team Leader/CDTL Angela Men) found that the application provided adequate justification for approval, although a tentative approval will be issued (see below).

Other then issues discussed in section 7, the following provides information that this reviewer believes are pertinent:

- While the principal PK studies provided in this application examined patients 18 years and older, discussions with OCP lead them to conclude that gastric emptying, intestinal

motility, and passive and active transport are fully mature in infants by approximately four months of age. Therefore, the absorption would not significantly differ in ages which are being requested in this application.

- OCP found no appreciable food effect.
- The Sponsor has provided a dog study to justify the absence of dose dumping. The Division previously recommended that the Sponsor provide human subject data on this issue. *In vitro* dissolution studies suggest the possibility of dose duping. Because of the latter observation and the absence of a human study, a contraindication for alcohol use will be recommended 6 hours prior to or after alcohol use.
- Between batch dissolution variability appeared wide. A one year provisional agreement for setting dissolution criteria was accepted by ONDQA, but additional actions are being requested to correct this problem.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical- Efficacy

As noted in the Background section of this review, after thorough discussions with the Sponsor, it was determined that the provided PK analysis was sufficient for the filing of this application. While the Sponsor was requested to provide the Division with a PK/PD analysis, the foundation of the consideration of the Sponsor's plan was the demonstration that PK was equivalent at numerous points during a 24 hour steady state maintenance period, in terms of cumulative AUCs and point concentrations as per FDA statistical bioequivalence ratio standards (i.e. the 90% C.I. of the ratio of the products are within the range of 80% to 125%). This provided a rationale that the shapes of the curves were not significantly different. With equivalence throughout much of the absorption curves over a 24 hour steady state maintenance period, it would be a reasonable to conclude pharmacodynamic identity to the referenced label drug (Topamax). This goes beyond the typical bioequivalence standard, which only considers the Cmax and AUC, and which would speak little of the general shape of the curve.

As the studies being used for consideration principally constitutes PK-like studies, these will be described in this section. Dr. Ta-Chen Wu was the primary reviewer of this information and Dr. Angela Men was the PK team leader as well as the CDTL for this application (considering its PK/PD nature).

The principal study (study 103) that was used to examine the similarity in curves between the referenced label drug, Topamax, and Trokendi XR was a single-center, multiple-dose, single-blind, randomized, two treatment, two-sequence, crossover study to evaluate the steady-state relative BA of 200 mg Trokendi XR (QD) compared to 100 mg Topamax tablet (BID, 12 hours apart). Thirty-nine patients were randomized and each sequence of the study included a 3 week titration period followed by a 10 day maintenance period. Examination of AUC and

Cmax, as well as Cmin, fulfilled routine bioequivalence standards. This information is presented in the table 1 (Transcribed from Dr. Wu's review) below.

Table.1 Summary of statistical analysis for relative bioavailability of 200-mg dose of Trokendi XR™ vs. TOPAMAX® at steady-state

Parameter	N	Trokendi XR XR™ (A) LS Mean	TOPAMAX® (B) LS Mean	Geometric Mean Ratio (A/B, %)	90% CI
AUC0–24 (ng·h/mL)	33	144000	149000	97.06	(94.01, 100.21)
Cmax,ss 0-24 (ng/mL)	33	6690	7600	88.01	(85.10, 91.02)
Cmin,ss (ng/mL)	33	5120	5130	99.91	(95.87, 104.13)

A crucial part of the Sponsors analysis is a very novel approach to examining the similarity of absorption curves presented in Figures 1 and 2[1]. Thus, the Sponsor provided additional analysis which is presented in Figure 1 below (transcribed from Dr. Wu's review). This figure presents data at numerous time points throughout a 24 hour observation period at steady state (day 31). The upper panel presents the mean concentration-time curves, and the lower panel presents a comparison of mean cumulative (partial) AUC ratios (Trokendi XR/Topamax) and their 90% CI (indicated by bars). As can be observed from the latter panel, all measured time points meet the statistical bioequivalence standard: i.e. all 90 % AUC confidence 90% CI lie within the range of 0.80 to 1.25.

[1] Note: A survey by OCP indicated that this analysis has not been performed for any other reviewed drug.

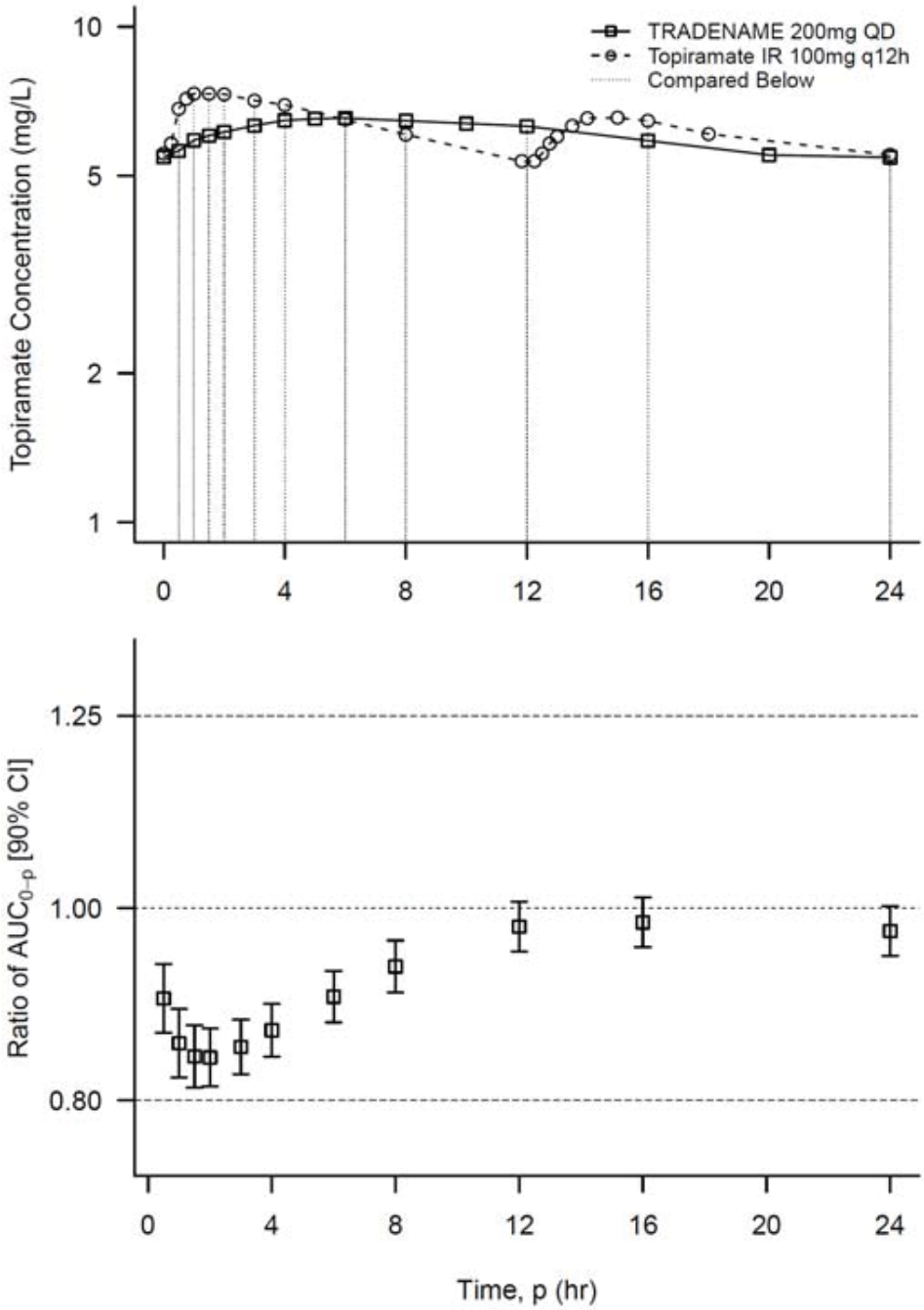


Figure 1 Steady state (day 31) mean plasma concentration-time curves (upper panel) and cumulative (partial) AUCs ratios with 90 % confidence intervals.

Figure 2 (transcribed form Dr. Wu's review) presents a comparison of mean point concentration ratios (Trokendi XR/Topamax) and their 90% CI (upper panel) and point-to-point[2] (partial) AUC ratios (Trokendi XR/Topamax) and their 90% CI (indicated by bars) for

[2] For reasons of illustration, with regard to the second panel, the point above 24 hours represents the ratio of AUCs from 16 to 24 hours.

the same time points presented in the previous figure. Again, similar bioavailability is observed throughout the 24 hour period with the exception of the first 90 minutes, where the lower range of the CIs fall slightly below these standards.

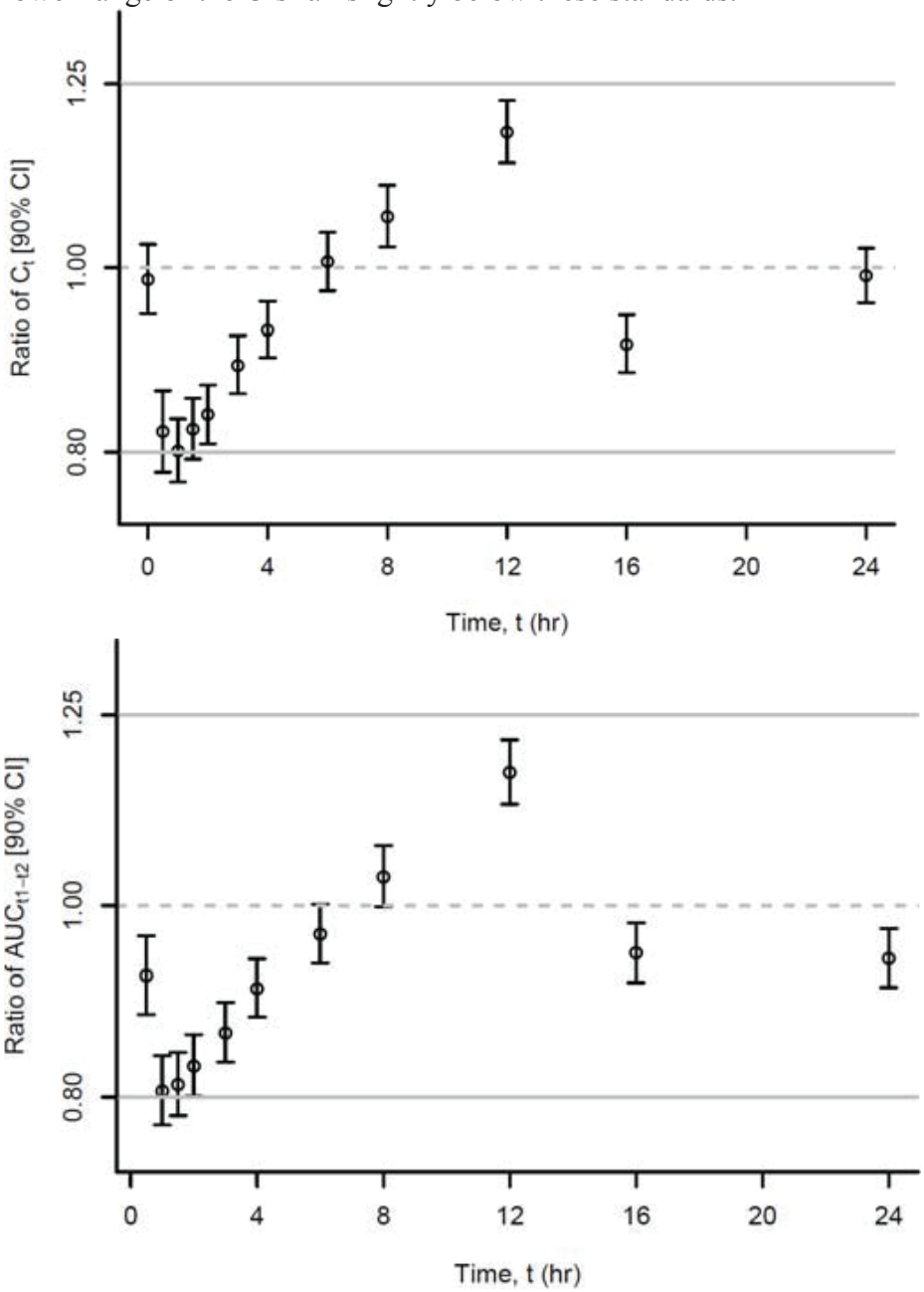


Figure 2 Steady State (day 31) concentration ratios with 90% confidence intervals (upper panel) and point to point AUC ratios with 90% confidence intervals (lower panel).

The analysis is unlike a simple examination of bioequivalence used for generics, as it examines similarity of absorption over multiple epochs for a full dosing cycle. While the examination did not demonstrate 100% fulfillment for the equivalence throughout the 24 hour dosing cycle it did demonstrate the equivalence for a very large percentage of this cycle (i.e.

94%). The Division believes that this, along with the demonstration of the more traditional bioequivalence standard described above, provides reasonable justification to conclude that shape of the curves do not significantly differ and thus pharmacodynamic equivalence can be concluded. Also it is noteworthy that while there is a brief period of lower concentrations, the analysis described is being used to determine the likelihood that a study using the same dosing will demonstrate efficacy at the intended prescribed doses, and not that the drugs would show absolute equivalence with regard to efficacy. I believe this analysis supports the former, but not necessarily the latter point.

Dr Wu notes that certain features of the concentration response relationship of topiramate are supportive of this conclusion. Thus, median percent reduction and percent responders were the greatest in the mid-range plasma topiramate concentrations from 3.2 to 5.4 μg/mL and from published data "optimal treatment response is most likely found between 2 mg/L and 10.5 mg/L." The range of exposures observed with Trokendi, as observed in Figure 2, is within the latter described ranges. Moreover, Dr. Wu notes that the fact that a lower percent fluctuation was observed for Trokendi XR™ (26%), compared to Topamax Tablets (40%) at steady-state in pivotal relative BA study and compared to most ER dosage forms of the approved AEDs, serves to support the Sponsor's argument. This reviewer believes that while these observations are helpful, the analysis presented in Figures 1 and 2 represents the crucial element of the Sponsor's argument. .

Other supportive factors for the above conclusion includes similar bioavailability for a 24 hour period of standard bioequivalence standards at a maintenance dose demonstrated in patients (study 108) who were converted from Topamax to Trokendi XR; albeit when broken down by patients on neutral and inducing drugs, the latter group was slightly below bioequivalence standards. Nonetheless, the inducing subgroup was too small (n=13) to allow for a reliable conclusion.

8. Safety

As noted above, this approval is based upon a demonstration of PK equivalency of Trokendi XR to the referenced label drug, Topamax. This should apply to both issues of safety as well as efficacy conclusion. The safety of this drug is therefore largely based upon the safety of the referenced label drug, Topamax. Nonetheless, Dr. Rusinowitz, the Medical Reviewer, and this Team Leader examined safety data provided in 11 studies, 10 in normal subjects and 1 in adult seizure patients. One additional pediatric study is ongoing in pediatric seizure patients, for which there was no data submitted.

A total of 359 normal healthy subjects enrolled in all studies. The studies in normal patients were principally targeted at the examination of PK parameters. All of PK studies in normal volunteers, except one, examined single dose exposures to Trokendi XR of 25 to 200 mg/day. The exception was study 103, which was a multiple-dose, randomized, single-blind (to subjects), two-treatment (Topamax/Trokendi XR) crossover study to determine the pharmacokinetic equivalence. Exposures to reference and test drug in this case involved a 3

week titration phase, followed by a 10 day maintenance phase (200 mg/day). Thirty-nine patients enrolled in the in this multiple dose study.

Dr. Rusinowitz and this reviewer performed a careful safety analysis was performed in the multiple dose study (study 103). As noted above, each phase of the crossover for this study included a 3 week titration period followed by a 10 day maintenance period at 200 mg/day (Topamax twice daily versus Trokendi XR once daily, respectively). The incidence and type of all treatment emergent adverse reactions were similar after dosing with Topamax or Trokendi XR, and similar experience with Topamax. Overall 33 of 34 and 30 of 38 of subjects taking Trokendi XR and topiramate experienced adverse events. No serious adverse events were observed in this study. Four subjects discontinued during Topamax treatment and 2 during Trokendi XR treatment. Of these only one, in each treatment, involved a discontinuation because of adverse events (one with headaches in the Topamax phase and one for cognitive changes in Trokendi XR phase). No serious adverse events were reported; albeit, of limited exposures, this study does not indicate any difference in the safety profile of Trokendi XR to the referenced label drug.

Off the complete new normal subject database, no deaths were observed and only one only one serious adverse event was observed. The latter was a patient who developed diverticulitis after treatment, which was not considered related to Trokendi XR. Five discontinuations as a result of AEs were noted in this database, only one of which was thought drug related (i.e. decreased concentration and attention span). These data did not suggest any differences to the reference label drug.

One open label study examined adult patients with epilepsy (study 108) who were on a stable dose of 200 to 400 mg/day Topamax as adjunctive or monotherapy. The protocol called for monitoring such patients for 2 weeks on Topamax and subsequently converting them to the same dose daily of Trokendi XR, following which they were monitored for an additional 2 weeks. While the primary endpoint was the examination of PK, secondary endpoints included safety. A total of 66 patients were studied. No deaths or SAEs were reported. One patient was noted to discontinue while on Topamax; this was thought secondary to a valproic acid reaction. Seizures were measured as a safety endpoint; there was no significance difference between the number of patients having seizures and the number of seizures that they had during the 2 weeks of Topamax and Trokendi XR treatment. Fewer patients were noted to experience AEs during the 2 weeks of Topamax observation (11%, n=7) then with Trokendi XR (39%, n=24). All AEs were classified as mild to moderate in severity. The Sponsor believed that the imbalance in AEs is a result of the study design: i.e. “imbalance may have been influenced both by the open-label and the sequential design of the study.” To further support the Sponsor’s argument, I would note that the balanced, healthy subject blinded, multiple dose study (study 103) indicated no differences between treatment arms.

In summary, the limited empirical data do not indicate any significant difference in the safety profile between Topamax and Trokendi XR. This, off course, is further supported by the extensive demonstration of the equivalence between the shapes of time/concentration and the resulting conclusion of this drugs pharmacodynamic similarity to Topamax.

9. Advisory Committee Meeting

None

10. Pediatrics

The referenced label drug, Topamax, which is available as both tablet and sprinkle capsules, is indicated for POS and PGTC seizures for both monotherapy and adjunctive therapy down to 2 years of age, and adjunctive treatment for seizures of LGS down to 2 years of age. In the present NDA, the Sponsor is requesting all indications (b) (4)

This Division met with the PERC Committee on 5/23/12 and agreed with the following principles to guide drug labeling and PREA requirements:

- Although the Sponsor contends that (b) (4) there was consensus by the committee and this Division that, because of the size of such capsules, it was unsafe to label the medication below 6 years old.
- Although the capsule can be opened, and a bioavailability study indicated that there is bioequivalence when mixed in apple sauce, it was determined that because the slow release nature of this formulation is dependent on the intact medication beads and that chewing can undermine this process, the medication could not be labeled for sprinkle use. The Sponsor was asked, in a previous communications, to developed a pediatric friendly formulation (e.g. a liquid formulation), or prove that due diligence was taken to develop such a formulation without success. The Sponsor has yet to provide this Division with an adequate response.
- Topamax used as monotherapy in children less then ages of 10 years old for POS and PGTC seizures is still patent protected, and cannot be indicated in the Trokendi XR label.

This has led to an agreement for the following pediatric indications:

- Partial Onset Seizure and Primary Generalized Tonic-Clonic Seizures:
  - Initial monotherapy in patients 10 years of age and older
  - Adjunctive therapy in patients 6 years of age and older.
- Adjunctive treatment in seizures associated with LGS in patients 6 years and older.

The following PREA issues/requirements were identified:

- The Sponsor should develop a child friendly XR formulation (e.g. liquid), with similar pharmacokinetic properties as Trokendi XR. If this is not possible they must demonstrate, with due diligence, that such an attempt was made.

- The following are waived because insufficient patients with the disorder can be identified and the consequent impracticality in performing such studies:
    - Adjunctive POS treatment in patients less then 1 month of age
    - Adjunctive PGTC seizure treatment patients less then 2 years of age.
- The following are deferred, to allow the Sponsor to develop a child friendly XR formulation (e.g. liquid), with similar properties as that demonstrated for Trokendi XR; if this is not possible they must demonstrate, with due diligence, that such an attempt was made:
    - Adjunctive POS pharmacokinetic, efficacy and safety treatment study in patients 1 month to 6 years.
    - Adjunctive PGTC seizure pharmacokinetic, efficacy and safety treatment study in patients 2 years to 6 years.
- The following are waived because such studies are considered unethical[3]:
    - Monotherapy studies in POS in patients 1 month to 6 years old
    - Monotherapy studies in PGTC seizures in patients 2 years to 6 years old.
- Seizures resulting form LGS is not considered a PREA issue as it is an orphan indication.

Of note, there is patent protected information in the proprietary label regarding safety outcomes in a 1 to 24 month study in children. During a carve out review for a generic topiramate IR product, this information was deemed crucial for the safe use of this product, and was therefore not removed from the generic label. As the Division has been advised that there is no legal authority allowing the maintenance of such information in a 505(b)(2) application, a tentative approval must be granted until this patent expires.

Also of note, the monotherapy indication for POS and PGTC seizures in the 2 to 10 year age group has patent protection. But, it is believed that this can be removed from the label without affecting this drugs safe use.

11. Other Relevant Regulatory Issues

The Sponsor has provided financial interest information for clinical investigators. The medical reviewer, Dr. Rusinowitz, reviewed this information. No proprietary interest in this product or significant equity in the Sponsor, as defined in 21 CFR 54.2(b) is apparent according to Dr Rusinowitz.

12. Labeling

[3] Note: The epilepsy community considers placebo control studies as unethical. While the Division is presently allowing for historical controls trial in adults, based upon well document historical control data, no such data exists for children, therefore such studies cannot be performed. If the new formulation, however, exhibits the same properties as that of the present formulation, this reviewer believes that a monotherapy indication may be possible.

See label included in the Division's action letter.

13. Recommendations/Risk Benefit Assessment

The Sponsor's application provides adequate information to justify proof of efficacy and safety. A tentative approval action, however, will have to be taken because of pediatric issues discussed in the pediatric section.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN HERSHKOWITZ
06/22/2012

Clinical Review

Application Type	NDA
Application Number	201635
Priority or Standard	Standard
Submit Date	August 30, 2011
Received Date	September 9, 2011
PDUFA Goal Date	July 9, 2012
Division/Office	DNP
Reviewer Name	Martin S. Rusinowitz, MD
Review Completion Date	May 14, 2012
Established Name	Topiramate Extended Release
(Proposed) Trade Name	Trokendi XR
Therapeutic Class	Anticonvulsant
Applicant	Supernus Pharmaceuticals, Inc
Formulation(s)	Extended Release Capsules 25 mg, 50 mg, 100 mg, 200 mg
Dosing Regimen	Once Daily
Indications	Monotherapy in Partial Onset or Primary Generalized Tonic-Clonic Seizures Adjuctive Therapy in Partial Onset Seizures, Primary Gerneralized Tonic-Clonic Seizures and Seizures Associated with Lennox-Gastaut Syndrome
Intended Population	Monotherapy, Patients ≥ 10 Years of Age Adjunctive Therapy, Patients ≥ 6 Years of Age

1. Introduction

Trokendi XR is the first extended-release (ER), once daily capsule formulation of topiramate for the treatment of patients with epilepsy. The immediate-release (IR) tablet formulation, Topomax (TPM), was originally approved in the US in December, 1996 (NDA 020505). Since then several generic versions of the IR formulation have been approved in this country.

Trokendi XR is intended for the same epilepsy indications as the immediate-release topiramate product, Topomax tablets, and for the same patient populations, with one exception: because Trokendi XR is intended to be taken as an intact capsule, Supernus is seeking an indication for patients with epilepsy (b) (4) TPM, as a tablet and sprinkle capsule formulation, is indicated for use in patients ages 2 years and older. As a 505(b)(2), this clinical pharmacology-based New Drug Application is targeting the same epilepsy indications as TPM, with the age exception noted above.

As such, Trokendi XR is an antiepileptic drug (AED) with a proposed indication for:

- Monotherapy epilepsy: Initial monotherapy in patients (b) (4) with partial onset or primary generalized tonic-clonic seizures.

- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients with partial onset seizures or primary generalized tonic-clonic seizures, and in patients (b) (4) with seizures associated with Lennox-Gastaut syndrome (LGS).

This NDA, submitted as a clinical pharmacology-based application for this particular molecule and drug delivery platform, is novel for the Division of Neurology Products.

Trokendi XR is an extended-release formulation that combines the Supernus' proprietary Microtrol® technology platform and TPM, a molecule with an intrinsically long elimination half-life. Although not literally "super-imposable", the PK profile at steady state generated by Trokendi XRs formulation administered once-daily in healthy volunteers appears similar to that of the TPM IR formulation administered twice-daily on the basis of the following observations:

- Bioavailability of the ER formulation relative to the IR formulation at steady state meets classical BE criteria for traditional PK parameters: Cmax, Cmin, and AUC.

- Fluctuation, the magnitude of the rise and fall of drug level in plasma relative to the average plasma level of the ER formulation is low.
- Within and between-subject variability of the ER formulation are low.

- Almost all time points throughout the 24-hour period of observation, the extent of absorption (assessed as “partial AUC”) for the ER relative to the IR falls within the bioequivalence range 0.80 to 1.25.

2. Background

While a 505(b) (2) submission, this NDA is unique in that Supernus is presenting a clinical pharmacology-based new drug application. This was initially discussed at an End of Phase II meeting on November 17, 2009. Supernus had contended that an extensive randomized clinical exposure to Trokendi XR and placebo is not necessary to conclude that a product with the clinical pharmacology attributes of Trokendi XR will have the same desired clinical activity as the immediate-release versions of the product already on the market. They claim that if a clinical pharmacology-based application is successfully submitted and reviewed that the need to expose clinical participants with epilepsy to titrating doses and placebo is no more necessary for this program than for an Abbreviated New Drug Application with a generic formulation.

At this meeting, Supernus presented data demonstrating the equivalence of Cmax, Cmin and AUC at steady state between the 200 mg dose of the IR formulation of TPM and its ER preparation in healthy normal volunteers. The data appears to indicate that Trokendi XR produces equivalent plasma concentrations to the IR preparation over all coincidental time points except for the first hour post-dose (quantified by the confidence limit of the ratio of IR / ER concentrations at each time point), throughout a 24-hour period. This appears to be consistent with previous applications for extended-release formulations of other antiepileptic drugs, Supernus proposed conducting a comparative bioavailability study at steady state with daily dosing of Trokendi XR vs BID dosing of the IR preparation at equivalent total daily doses of 100-400mg in patients. If this study confirmed the equivalence of key pharmacokinetic parameters between the two products in healthy normal volunteers they requested that it be adequate to support a 505(b)(2) marketing application.

At this same meeting DNP voiced concern that despite possible bioequivalency, the curves of plasma concentration vs. time for the IR and ER preparations appear, on-face, to not be superimposible. The Division questioned whether the difference between the shapes of these curves might be better compared using slopes at the multiple time points. DNP was not aware of any convincing empirically based data that indicates that the rate of rise in the serum

concentration has no pharmacodynamic significance and suggested that this issue be addressed. It was therefore recommended that Supernus either present an analysis for the equivalence of the slopes, and a justification for such an analysis, or a convincing empirically based argument that illuminates the lack of pharmacodynamic significance for the serum rate of rise and fall in this disorder.

Another meeting was scheduled between the FDA and Supernus on February 8, 2010. This meeting was cancelled because of inclement weather, but the issues to be discussed were reviewed in preliminary comments (questions and answers) which were received by Supernus. In this, Supurnus felt that they had provided a scientific rationale to address the request of the agency for identification of parameters under which a TPM controlled release product could be approved for marketing following a clinical conversion pharmacokinetic study in the target population instead of a traditional placebo controlled efficacy study.

The Division acknowledged that Supernus had provided a comprehensive argument to support their position and that DNP was unaware of any additional existing data that could be reasonably brought to bear to support their view. It was noted, however, that there remained little evidence that speaks directly and specifically to the contribution (if any) of the shape of the plasma concentration-time curve to the effectiveness of the product. This deficiency not withstanding, the Division admitted that Supernus' argument is sufficient to support a filing of an application for this new dosage form but the ultimate response to the submission would, of course, be a matter of review. DNP also noted that they did not believe that it is necessary to perform the proposed clinical conversion study. Although it might address the important question of what the plasma levels will be in the hours and days immediately after conversion to Trokendi XR from the immediate release formulation, it was believed that these answers might be obtained through simulations provided the compartmental pharmacokinetic analysis can ensure that the data is well described.

At a final Pre-NDA meeting, held on September 2, 2010, Supernus confirmed the studies planned for inclusion in its NDA. The Agency recommended that the Sponsor submit all of the PK datasets, including raw data and PK parameters, in SAS transport files. Lastly, the Division indicated that the rationale for conducting an in-vivo alcohol-drug interaction study was not clear. Results of such a study in dogs, rather than humans, are not acceptable from an OCP perspective. DNP recommended that an alcohol-drug interaction study in humans, instead of dogs, be completed. This, though, was deemed a review and not a filing issue.

After the NDAs submission and preliminary review, the initial NDA was deemed not sufficiently complete to permit a substantive review and a Refuse-to-File letter was issued on March 14, 2011. All the refuse to file issues were limited to CMC problems. The reapplication was received on September 9, 2011 and finally filed on November 8, 2011.

3. CMC

Dr. Martha Heimann, CMC Lead, had initially found this application to not be fileable because of lack of analytical procedures to be used for acceptance testing. The specifications needed to include adequate tests and analytical procedures to allow verification of each parameter reported on the manufacturer's certificate of analysis. Additionally, the proposed composition, manufacturing process and controls for the commercial product had not been provided.

These deficiencies were apparently corrected and Dr. Heimann's CMC review will detail any remaining CMC issues.

4. Nonclinical Pharmacology/Toxicology

Dr. Ed Fisher found the application to be fileable. His review will detail nonclinical pharmacology and toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

In this submission the Sponsor is presenting a clinical pharmacology-based new drug application by demonstrating the bioequivalence for time-point to time-point within the 24 hours at steady-state between once-daily Trokendi XR and approved IR tablets (BID). The clinical program consists of 8 studies in healthy adult volunteers to support this NDA, as well as 2 ongoing studies in epilepsy patients, as summarized below:

- Study 538P109: PK comparison between young and elderly adult patients; single 100mg dose

- 7 Biopharm studies: establish steady-state BA/BE vs. IR, dose linearity/proportionality, food effect (200 mg),and BE between the clinical and registration scale formulations (50, 100, and 200 mg)

- Study 538P108: a conversion study from TPM IR (on either 200, 250, 300, 350, or 400 mg/day, BID) to Trokendi XR in epilepsy patients (N=62); steady-state PK (day 14 of IR vs. 24 hour of Trokendi XR)

- Study 538P107: examines the PK profile of Trokendi XR in pediatric epileptic population and is ongoing

The following Sponsor's table shows all studies referenced in this application.

Study ID	Primary Endpoint or Endpoints	Location of Study Report	Study Objective	Study Design	Study & Control Drugs/ Dose/ Route/ Regimen	# Subjects by Arm Entered/ Completed	# Sites / Subject type	Duration	Study Status/ Study conduct dates
538P103	PK	Module 5, Section 5.3.3	Steady state PK	Comparative, randomized, multiple dose, 2-treatment, 2-sequence, 2-period crossover with active control	A: TPM CR[1] 200mg x 10 days (after 3 weeks titration) B: Topamax 200mg x 10 days (after 3 weeks titration)	39 subjects enrolled, 33 subjects completed	Single center/ Healthy, normal	10 day maintenance with 21 day titration per treatment period	Complete 09 Mar 2009- 09 Aug 2009
538P104	PK	Module 5, Section 5.3.3	Dose proportionality	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 8 x 25mg B: TPM CR 4 x 50mg C: TPM CR 2 x 100mg D: TPM CR 1 x 200mg	34 subjects enrolled 24 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods	Complete 16 Jul 2008 -18 Nov 2008
538P104 .5	PK	Module 5, Section 5.3.3	Dose linearity	Comparative, randomized, multiple dose, 4-treatment, 4-sequence, 4-period crossover study	A: TPM CR 25mg B: TPM CR 50mg C: TPM CR 100mg D: TPM CR 200mg	36 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 4 treatment periods	Complete 16 Jul 2008 -18 Nov 2008
538P105	PK	Module 5, Section 5.3.3	Food effect	Comparative, randomized, single dose, 2-treatment, 2-sequence, 2-period crossover study	A: TPM CR 200mg, fasted B: TPM CR 200mg, fed	32 subjects enrolled 28 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods	Complete 23 Oct 2008-23 Dec 2008
538P106	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 100mg, Clinical lot B: TPM CR 100mg, CMO lot	28 subjects enrolled, 27 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods	Complete 27 Apr 2010- 31 May 2010
538P106 -50	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 50mg, Clinical lot B: TPM CR 50mg, CMO lot	32 subjects enrolled 31 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods	Complete 10 Oct 2010 – 05 Nov 2010
538P106 -200	PK	Module 5, Section 5.3.3	Bridging different manufacturing sites	Comparative, randomized single-dose, 2-period, 2-sequence crossover study.	A: TPM CR 200mg, Clinical lot B: TPM CR 200mg, CMO lot	32 subjects enrolled 32 subjects completed	Single center/ Healthy, normal	Single dose, 2 treatment periods	Complete 01 Oct 2010- 25 Oct 2010
538P109	PK	Module 5, Section 5.3.3	Young vs. Elderly	Comparative, single-dose, parallel group study	TPM CR 100mg, fasted	18 young adults enrolled and completed, 13 elderly enrolled and completed	Single center/ Healthy, normal young and elderly	Single dose, 1 treatment period	Complete 03 Jun 2010– 16 Jul 2010
538P108	BA	Module 5, Section 5.3.1.2	PK of IR to ER Switch	Multi-center, open-label, two-treatment, single sequence conversion study	TPM ER – equivalent to current therapy TPM IR – equivalent to current therapy	62 patients with epilepsy (72 planned)	11 centers, adults with epilepsy on treatment with TPM	4 weeks.	Complete: 11 July 2010 – 23 Jan 2011
538P107	PK	Pending	Pediatric PK	Multi-center, open-label, switch to ER	TPM ER – equivalent to current therapy	Approximately 40 male and female pediatric subjects ages 4-17	Up to 15 centers, children with epilepsy on treatment with TPM	2 weeks	Ongoing
538P106 A	PK	Pending	Bridging different manufactured lots	Single-dose, open-label, randomized, 2-treatment, 2-period, 2-sequence crossover study.	Two lots of TPM ER 50mg	Up to 32 male and female subjects	Single center/Healthy normal	Single dose, two treatment periods	Ongoing
538P106 B	PK	Pending	Bridging different manufactured lots	Single-dose, open-label, randomized, 2-treatment, 2-period, 2-sequence crossover study.	Two lots of TPM ER 100mg	Up to 32 male and female subjects	Single center/Healthy normal	Single dose, two treatment periods	To be initiated (as of 14July11)
538P106 C	PK	Pending	Bridging different manufactured lots	Single-dose, open-label, randomized, 2-treatment, 2-period, 2-sequence crossover study.	Two lots of TPM ER 200mg	Up to 32 male and female subjects	Single center/Healthy normal	Single dose, two treatment periods	To be initiated (as of 14July 11)

Dr. Ta-Chen Wu, clinical pharmacologist, will provide a further definitive review of this clinical pharmacology-based NDA.

Dr. Arzu Selen, biopharmaceutics, will provide further review of issues previously identified, such as those involving the dissolution method development provided in the submissions which does not provide *in vitro* product characterization with respect to drug release in conditions mimicking the GI environment. Additionally, an applesauce study will be assessed regarding the in vitro product performance after the product is kept in apple sauce, as well as its stability in other soft foods.

6. Clinical Microbiology

None

7. Clinical/Statistical – Efficacy

Supernus has developed a once-daily formulation of TPM. At present, TPM is typically administered twice-daily. Although its precise mechanism of action is unknown, TPM is considered to produce its antiepileptic effects through an inhibitory activity of kainate/α-amino-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)-type glutamate receptors, enhancement of γ-amino butyric acid (GABA)-ergic activity, inhibition of voltage-sensitive sodium and calcium channels, increases in potassium conductance and inhibition of carbonic anhydrase.

The clinical efficacy of TPM has been investigated and proven in numerous trials: approved dosages (i.e. ≤ 400mg/day) of TPM as monotherapy or adjunctive therapy were effective in reducing the frequency of seizures in patients with primary generalized tonic clonic seizures, partial seizures or seizures associated with Lennox-Gastaut syndrome. After six or seven months of TPM monotherapy in dosage comparison and noncomparative trials, 44-83% of patients were seizure-free, and after 12 or 13 months, 41- 76% of patients were seizure-free. In subgroup analyses, TPM was shown to be effective in pediatric and elderly populations and in treating both partial and generalized epilepsies.

TPM is also effective as an adjunctive AED. In randomized, double-blind trials in adult and/or pediatric patients with primary generalized tonic-clonic seizures or partial seizures, approved dosages of TPM were generally significantly more effective than placebo in reducing the median seizure frequency from baseline following treatment for 8-12 weeks (reduction of 30-57% vs 9-13%). In patients with Lennox-Gastaut syndrome, the frequency of drop seizures decreased by 15% in TPM recipients and increased by 5% in placebo recipients. TPM provides long-term seizure control; patients with epilepsy receiving TPM had 41-71% reductions from baseline in seizures in non-comparative trials of > 6 months duration.

Supernus speculates, based on a lack of empirical evidence, that when comparing the bioequivalence of a once-daily regimen of an extended release TPM compared to a twice-daily dosing regimen of immediate release TPM that the rate of rise and fall in the plasma concentration of TPM has no pharmacodynamic significance in treating epileptic seizures. The Sponsor further posits that while it is unknown whether or not transient fluctuations in plasma levels of TPM are relevant to TPM's pharmacological action and overall clinical efficacy, the magnitude of these fluctuations is known to be relatively small, and this magnitude should be a primary consideration when assessing the possible relevance of these transient fluctuations.

Supernus further speculates, since extended/controlled-release versions of other AEDs have been approved in the recent past (carbamazepine, valproic acid, levetiracetam, and lamotrigine), that from a purely logical point of view none of them - whether approved based on efficacy demonstrated in placebo-controlled randomized clinical trials in refractory epilepsy patients or whether approved mainly based on pharmacokinetic considerations - provides convincing supportive evidence of the hypothesis that a change in the shape of the pharmacokinetic curve affects pharmacodynamics.

Trokendi XR is an extended-release formulation that combines the Supernus' proprietary Microtrol® technology platform and TPM, a molecule with an intrinsically long elimination half-life. Although not literally "super-imposable", the PK profile at steady state generated by Trokendi XRs formulation administered once-daily in healthy volunteers is highly similar to that of the TPM IR formulation administered twice-daily on the basis of the following observations:

- Bioavailability of the ER formulation relative to the IR formulation at steady state meets classical BE criteria for traditional PK parameters: Cmax, Cmin, and AUC.
- Fluctuation, the magnitude of the rise and fall of drug level in plasma relative to the average plasma level of the ER formulation is low.
- Within and between-subject variability of the ER formulation are low.
- Almost all time points throughout the 24-hour period of observation, the extent of absorption (assessed as "partial AUC") for the ER relative to the IR falls within the bioequivalence range 0.80 to 1.25.

The Sponsor's figure, below, demonstrates the Concentration vs. Time profiles for Trokendi XR and immediate-release TPM at steady state in healthy volunteers.

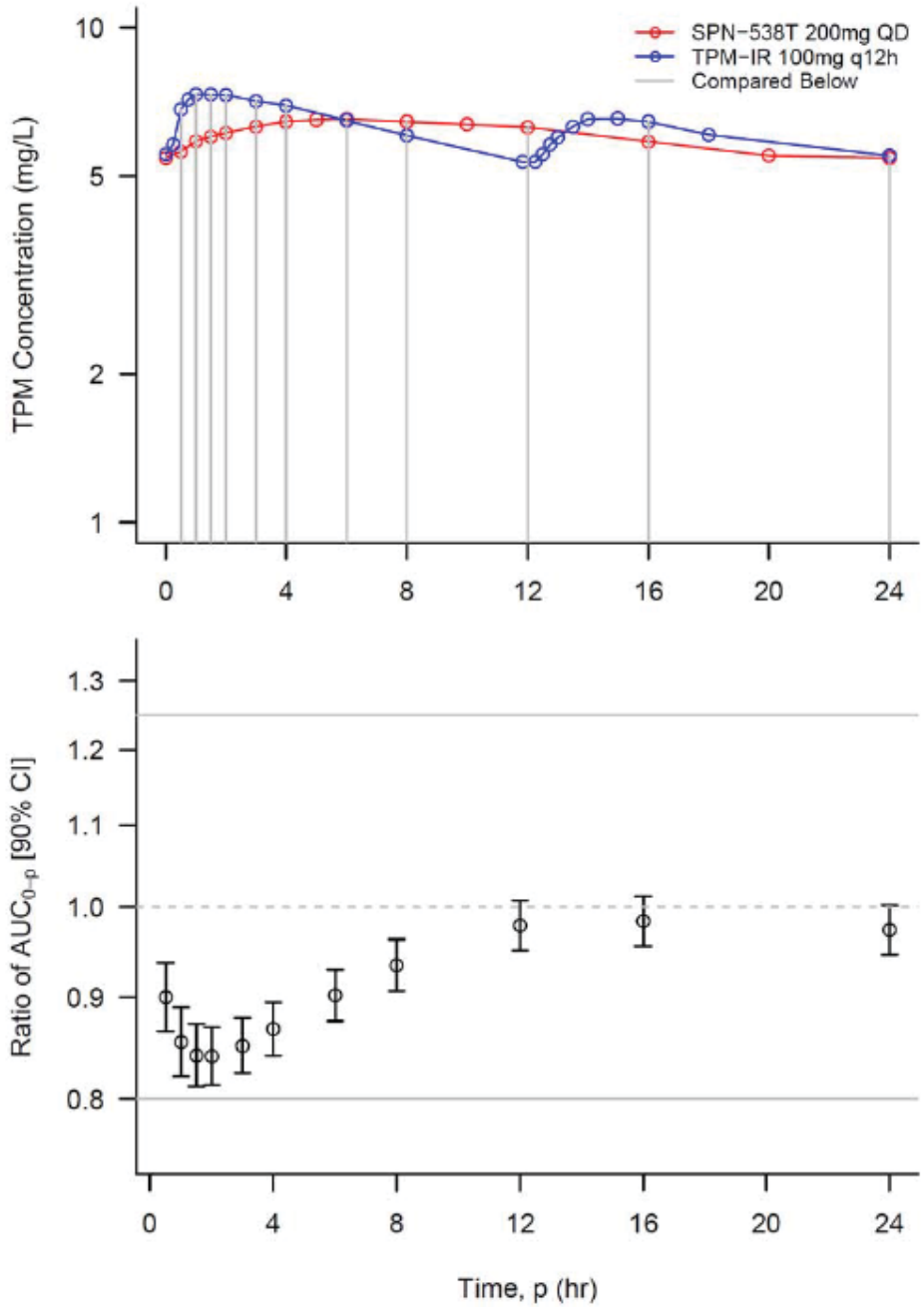


Figure 1: ***Upper Panel*****: Concentration vs Time profiles for SPN-538T and TPM-IR at steady state in healthy volunteers.**
Grey lines indicate coincidental time points for which the partial AUC is compared in the lower panel. Lower Panel: The point estimate and 90% confidence intervals for the ratio of partial AUC (AUC0-p) for SPN-538T relative to TPM-IR form (538P103, 2009).

The Sponsor's figure, below, presents the pharmacokinetic profiles for the IR and ER formulations of two Supernus AEDs under development, TPM, and oxcarbazepine as well as profiles of two AEDs for which ER dosage forms are approved, lamotrigine and levetiracetam.

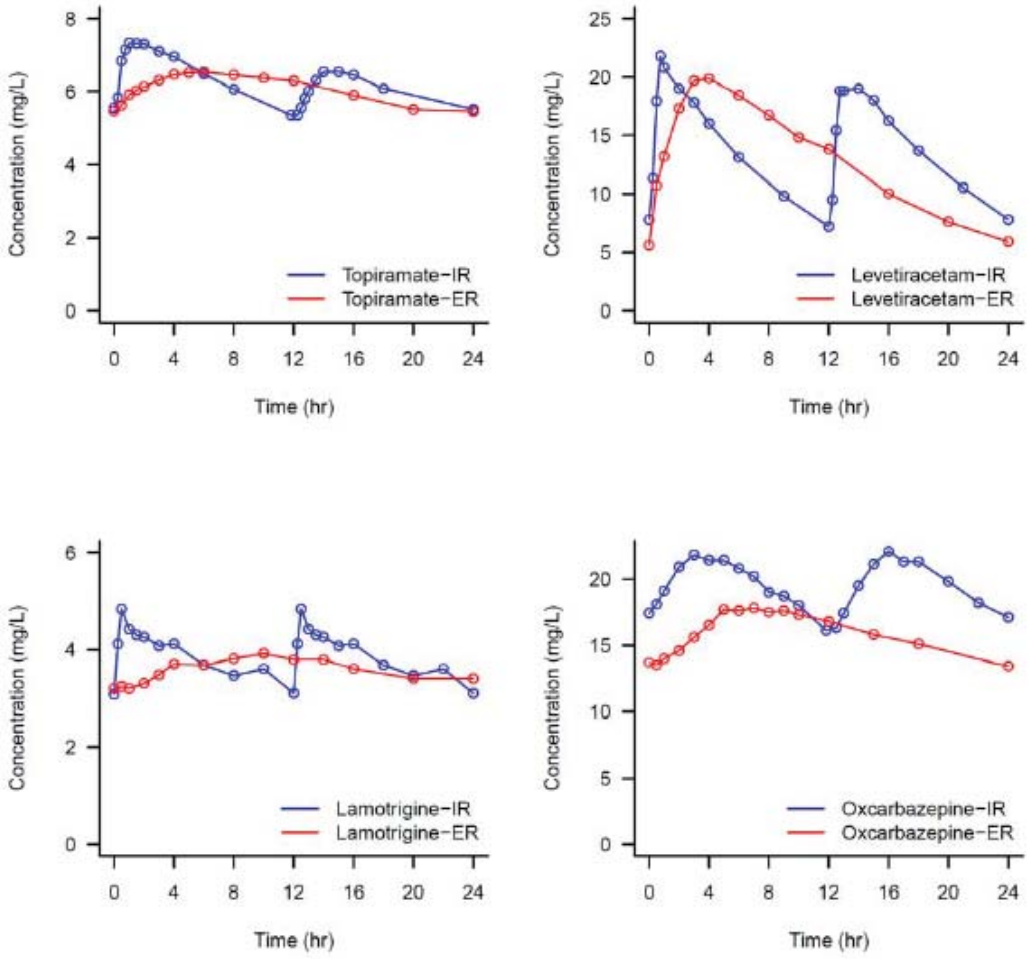


Figure 2: Concentration *vs.* time curves for IR and ER dosage forms of four AEDs.
Topiramate (538P103 2009), levetiracetam (KEPPRA® XR Review), lamotrigine (LAMICTAL® XR Review), and oxcarbazepine (804P103 2007; MHD shown).

The comparative bioavailability of the ER formulations of these four AEDs relative to their IR formulations are compared. For TPM, the ratios and 90% confidence intervals for Cmax, Cmin and AUC all fall within the range 0.80 to 1.25. For lamotrigine, only Cmin falls within this range, and for levetiracetam, only AUC. For oxcarbazepine the confidence intervals fall below the BE range for all three parameters. Of the four drugs, only Trokendi XR meets the classical BE criteria for all three parameters.

Based on these empirical findings, the Sponsor further speculates that, from a pharmacokinetic standpoint, changes in the shape of the PK profile are related to the accumulation factor (fluctuation) of the drug, the bioavailability of the ER formulation relative to the IR formulation, and the variability of the dosage form. For a drug with a high accumulation factor (therefore long elimination half-life and low fluctuation at steady state), presented as an ER formulation having bioavailability similar to the IR and a low inter- and intra-subject variability, the rate or extent of absorption of the drug is likely to have relatively little impact on the shape of the PK curves. Similarity of partial AUCs between formulations (as assessed using the BE statistical standards) implies that the amount of available drug at any given time-point is comparable between the two formulations according to the classical BE criteria. This is basically due to the fact that, while the slopes of the IR vs ER curves at steady state are on face different, the fluctuations related to the entry of drug into the circulation during the absorption phase occur on top of a significant amount of drug already accumulated in the systemic circulation, as represented by the almost identical Cmin values.

8. Safety

Eight clinical studies (studies 538P106A,B and C counted as one study) were conducted in healthy volunteers and one 2 in subjects with epilepsy. Only one (538P103-steady state PK study) was a blinded. The following sponsor's table lists the studies and subjects included in the safety analyses. Detailed descriptions of these numbered studies can be found in the efficacy review section above.

		Number of Subjects		
Study	**Study Type**	**Enrolled**	**with SAEs**	**Discontinued due to AEs**
Healthy Volunteer Population				
538P103	Steady-state PK	39	0	2
538P104	Dose Proportionality	34	0	1
538P104.5	Dose Linearity	36	1	1
538P105	Food Effect	32	0	0
538P106	Bridging manufacturers	28	0	0
538P106-50	Bridging manufacturers	32	0	1
538P106-200	Bridging manufacturers	32	0	0
538P109	Elderly	31	0	0
538P106A	Lot Comparison	31	0	0
538P106B	Lot Comparison	32	0	0
538P106C	Lot Comparison	32	0	0
Total Healthy		***359***	***1***	***5***
Epilepsy Population				
538P108	Adult PK, Switching	66	0	1
538P107	Pediatric PK, Switching	24	0	0
Total Epilepsy		***90***	***0***	***1***

Of the 8 pharmacokenetic studies, all but one were single-dose studies, although in most studies - due to their cross-over design - most subjects received more than one treatment. Doses ranged from 25mg to 200mg, with 200mg being the most commonly administered single dose.

The only multiple dose study was 538P103, *A Single-Center, Multiple-Dose, Randomized, Single-Blind, Two-Treatment Crossover Study to Determine the Pharmacokinetic Profile of SPN-538 Capsules Relative to Topamax Tablets in Healthy Adult Volunteers.* This was the only study where a limited direct safety and tolerability comparison between the IR form of TPM and Trokendi XR was performed.

A total of 335 adverse events (AE) were reported in this study; 33 subjects (97.1%) reported at least one adverse event after Trokendi XR dosing and 30 subjects (78.9%) reported at least one adverse event after TPM dosing. The incidence and number of events related to treatment were similar after dosing with each one. Paresthesias, headache, disturbance in attention, somnolence, and dysgeusia were the most frequently reported adverse events. Eight (21%) subjects receiving TPM experienced either dizziness or postural dizziness, compared to none of the 34 subjects receiving Trokendi XR. Overall, the range and severity of adverse events reported in the eight studies were within those expected for topiramate. There were no deaths and only one Serious Adverse Event (SAE): Subject 09 in Study 538P104.5 (dose linearity study) was hospitalized for an episode of diverticulitis considered by the investigator to be unrelated to the study drug. A total of five subjects discontinued from four studies due to AEs; only one of these discontinuations who experienced decreased concentration and attention span following administration of the study drug was considered related. The other AEs resulting in discontinuation were stress and headache following a motor vehicle accident, fever and sore throat and the SAE of diverticulitis mentioned above.

Only one trial, 538P108 (adult PK switching study) was conducted in 66 epilepsy patients on treatment with IR TPM as adjunctive or monotherapy. Subjects were switched to an equivalent dose of TOPAMAX (BID) for two weeks, and then switched again to the equivalent dose of Trokendi XR (QD) for two weeks. This was an open label study. One patient discontinued treatment with TOPAMAX® after experiencing an unrelated moderate AE due to toxicity of valproic acid, a concomitant medication. Although nine subjects experienced related AEs while taking Trokendi XR compared to one subject taking TOPAMAX, only two events were experienced by more than one subject (four subjects with headaches and two with fatigue). All AEs resolved within four to five days of Trokendi XR administration. Subjects were switched to an equivalent dose of TOPAMAX (BID) for two weeks, and then switched again to the equivalent dose of Trokendi XR (QD) for two weeks. This was an open label study.

Seven patients (10.6%) treated with TOPOMAX experienced at least one AE vs. 24 subjects (38.7%) treated with Trokendi XR. All AEs were moderate in severity and no subject experienced an SAE. All were consistent with the expected safety and tolerability profile for topiramate.

No safety and tolerability signals emerged to suggest any noticeable clinical difference from safety and tolerability profile of topiramate immediate-release product.

9. Advisory Committee Meeting

None

10. Pediatrics

The originally submitted NDA, which resulted in a Refuse-to-File response, requested labeling for monotherapy in ages greater than 10 years and adjunctive therapy (b) (4) The present resubmitted NDA asks for labeling of (b) (4) for both monotherapy and adjunctive therapy. There is one ongoing pediatric study, Protocol 538P107 titled "Evaluation of the Pharmacookinetic, Safety and Tolerability of TOP XR as Adjunctive Therapy in Pediatric Subjects with Epilepsy" which was submitted on October 21, 2010 as Submission 0027. This study has a current enrollment of 28 subjects and the age grouping has been skewed towards older participants with 21 subjects at ages 12 to 17 years, 7 subjects at ages 6 to 11 years and no subjects under the age of 6 years.

For reasons which are not clear to this Reviewer, the possibility of sprinkling the capsule contents on food was evaluated with a limited, preliminary evaluation of the pharmacokinetics of the product when removed from the capsule and sprinkled on apple sauce. Administration of the intact Trokendi XR 100mg capsules or sprinkling of the capsule contents led to similar exposure in young adult subjects. When capsule contents were administered in applesauce to 18 young adult subjects (age 19 45 years), plasma topiramate AUC0 inf and Cmax were 94% and 86% relative to those observed following administration of intact capsules.

This brings up the issue of the need for a specific pediatric formulation (perhaps a delayed release liquid) since there are a number of limiting issues relating to sprinkling the capsule contents on food for children ages 6 months to 4 years (and an even greater need for infants ages 1 month to 6 months). The present label specifically states that the capsule should not be opened. Additionally, there remains the issue of the capsule granules being chewed if the contents of the capsule were put in to apple sauce, particularly by younger children. This

would likely result in a toxic serum concentration of topiramate in the immediate hours after dosing and a sub therapeutic anticonvulsant serum concentration of topiramate later in the day, possibly resulting in break-through seizures.

Addressing the issue of a delayed release liquid preparation for children from 1 month to 4 years (and likely older as a practical point of view) was requested in a previous letter from the Agency but has not yet been addressed by the Sponsor. The need for such a a formulation, or proof that due diligence was taken to develop such a formulation has not been successful, has been agreed to as a PREA requirement.

DNP met with the Pediatric Review Committee (PeRC) on May 23, 2012 and agreed with the following principles regarding drug labeling and additional PREA requirements:

- Given the relatively large size of the Trokendi XR capsule, the Committee and DNP felt it was unsafe to label the medication below 6 years of age.

- Topomax monotherapy in children less than 10 years of age for partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTC) is still patent protected and cannot be indicated in the Trokendi XR label.

The pediatric indications are:

- POS and PGTC Seizures:

    - Initial monotherapy in patients 10 years of age and older
    - Adjunctive therapy in patients 6 years of age and older

- Adjunctive treatment in seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 6 years and older:

- The following indications were waived because of insufficient patients with the disorder:

    - Adjunctive POS treatment in patients less than 1 month of age
    - Adjunctive PGTC seizure treatment in patients less than 2 years of age

- The following are deferred in order to allow the Sponsor to develop a liquid formulation as described above:

    - Adjunctive POS pharmacokinetic, efficacy and safety study in patients 1 month to 6 years.

    - Adjunctive PGTC pharmacokinetic, efficacy and safety study in patients 2 years to 6 years.

- The following monotherapy studies are waived as placebo controlled epilepsy studies are considered unethical:

    - POS in patients 1 month to 6 years of age.
    - PGTC seizures in patients 2 years to 6 years of age.

- Seizures from LGS are not considered a PREA issue as it is an orphan indication

Addressing the issue of a delayed release liquid preparation for children from 1 month to 4 years (and likely older as a practical point of view) was requested in a previous letter from the Agency but has not yet been addressed by the Sponsor.

11. Other Relevant Regulatory Issues

The Sponsor has provided financial interest information for clinical investigators participating in studies included in this New Drug Application. None of the investigators have disclosed any proprietary interest in this product or any significant equity in the Sponsor as defined in 21 CFR 54.2(b).

12. Labeling

The draft labeling text Working Version is included as an appendix below.

13. Recommendations on Regulatory Action

This 505(b)(2) is a clinical pharmacology-based new drug application. This Reviewer is convinced that the bioequivalence for time-point to time-point within the 24 hours at steady-state between once-daily Trokendi XR and approved IR tablets (BID) has been adequately demonstrated. Furthermore, there is no clinical evidence to suggest that the pharmacodynamic anticonvulsive effect of Trokendi XR would be any different than a BID regimen of TPM IR.

I recommend approval for Trokendi XR 25, 50, 100 and 200 mg. capsules as both initial monotherapy in patients ≥ 10 years of age with partial onset or primary generalized tonic-clonic seizures as well as adjunctive therapy for adults and pediatric patients (>6 years of age) with partial onset seizures or primary

generalized tonic-clonic seizures, and in patients ≥ 6 years of age with seizures associated with Lennox-Gastaut syndrome (LGS).

Martin S. Rusinowitz, MD
Medical Reviewer
Division of Neurology Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN S RUSINOWITZ
06/20/2012

NORMAN HERSHKOWITZ
06/22/2012